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Application of Orphan Drug Designation to Cancer Treatments: A Comparative Study of the US and EU

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Guarantor: Vokinger

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Abstract

Objective: To determine differences in the characteristics of cancer drugs designated as Orphan Drugs by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Design and setting: Identification of all cancer drugs (initial or supplementary indication) with orphan status approved by the FDA between 2008-2017 based on publicly accessible reports. The European public assessment reports (EPAR) was searched to determine whether these FDA-approved drugs were also approved by the EMA.

Main outcome measures: Extraction of active ingredient, trade name, approval date, and approved indication from two FDA data sources (Orphan Drug Product Designation Database and Drugs@FDA) and comparison with the same data from EPAR.

Results: The FDA approved 135 cancer drugs with orphan indications that met our inclusion criteria, of which 101 (75%) were also approved by the EMA. 80/101 were first approved in the US. Only 41/101 also received orphan designation by the EMA. 33/101 were approved for biomarker-based indications in the US, however, only 9 approved cancer drug indications by the EMA were biomarker-derived drugs. 78% of approved cancer drugs that were only approved in the US with orphan status were indicated for solid tumors, 22% had indications for non-solid tumors. By contrast, out of those approved cancer drugs that received orphan designation by both Agencies, 20% were indicated for solid, and 80% for non-solid tumors.

Conclusions: Orphan designation was intended to encourage drug development for rare conditions. This study shows that the FDA approves more cancer drugs with orphan designations compared to the EMA, especially for subgroups of more prevalent cancers. One reason for the difference could be that the EU requires demonstration of significant benefit for drugs that target the same indication as a drug already on the market to earn the orphan designation; the US might consider adopting this policy.

Strengths and Limitations of this Study

Strengths:

- Our methodological and comparative approach (empirical analysis, health policy, comparative health law) enables to find possible solutions of how the US could adopt useful policies applied in the EU and thus improve the development of innovative cancer drugs.
- The inclusion of approved cancer drugs designated with orphan status over a time period of 10 years enables to detect informative trends in the specific jurisdiction (US and EU) as well as meaningful comparisons between the jurisdictions.
- To date, no study analyzed the differences in the application of orphan status on cancer drugs by the FDA and EMA.

Limitations:

- Our study is restricted to cancer drugs, and so is not generalizable to other drug classes.
- We did not investigate whether all approved cancer drugs with orphan designation by the EMA between those same years also received orphan status by the FDA. Therefore, it may be possible that certain cancer drugs with orphan designation by the EMA did not get orphan designation by the FDA.

Introduction

The US Congress passed the Orphan Drug Act in 1983 to create incentives for the development of drugs for rare diseases that might not otherwise be financially viable due to small potential patient populations.[1, 2, 3] Among other things, the statutory incentives include providing manufacturers with the opportunity to earn special tax breaks for research investment and the exclusive right to market orphan-designated drugs for 7 years from the date of marketing approval.[1, 5] Such market exclusivity would allow manufacturers to charge high prices for their rare disease drug product even in the absence of patent protection.[5] Pharmaceutical companies can apply for orphan drug designation from the Food and Drug Administration (FDA) based on either showing that the targeted condition affects fewer than 200,000 patients annually in the US, or showing no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the US, along with providing a medically plausible basis for believing that the drug would aid in the condition's treatment, prevention, or diagnosis.[6, 7]

In the European Union (EU), the European Medicines Agency (EMA) also designates drugs that target rare diseases with special status.[8] To qualify, a drug must be intended for the treatment of a disease that is life-threatening or chronically debilitating with an EU prevalence of less than 5 in 10,000, or it must be unlikely that marketing of the drug would generate sufficient returns to justify the investment needed for its development.[9, 10] In addition, no satisfactory method of treatment of the condition concerned is already on the market, or, if such a method exists, the new drug must be of significant benefit to those affected by the condition.[7] Like in the US, sponsors of designated rare disease drugs in the EU earn certain incentives, including administrative regulatory fee reductions and market exclusivity.[7, 11, 12] Thus, while most prerequisites for rare disease drug designation between the US and the EU are comparable, the major difference is that the EU requires demonstration of significant benefit in case the drug targets the same indication as a drug already on the market.

To determine whether differences in the design of the Orphan Drug Act in the US and EU lead to variations in the application of the statutory incentives, we reviewed all cancer drugs for which indications have been approved with orphan status between 2008 – 2017 by the FDA and then determined whether these cancer drugs had also been approved with orphan status by the EMA.

Methods

We first identified all cancer drugs with orphan status approved by the FDA between 1 January 2008 and 31 December 2017. The approval could have been for an initial or supplementary indication. Cancer drugs with approval for different indications were counted separately for each cancer indication. For example, bevacizumab (Avastin) was approved with orphan drug status for, among other things, treatment of patients with ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and glioblastoma. Cancer drugs with orphan status that were approved by the FDA for benign tumors as well as combined therapies (e.g., dabrafenib and trametinib [Mekinist]) were not included in our analysis. From two FDA data sources—the Orphan Drug Product Designation Database and Drugs@FDA—we extracted the active ingredient, trade name, orphan designation, approval date, and approved indication.

We then searched on the database of the EMA, the European public assessment reports (EPAR), to determine whether the FDA-approved cancer drugs with orphan status in our cohort were also approved by the EMA as of 1 August 2018. If so, we extracted the same data as from the FDA sources.

Results

The FDA approved 135 cancer drug indications with orphan designations that met our inclusion criteria. Among this sample, 101 (75%) were also approved by the EMA by 1 August 2018, including drugs with and without orphan drug designation by the EMA (see **Appendix**). Two indications were refused market approval in the EU: romidepsin (Istodax) was refused for treatment of non-Hodgkin's lymphoma, and pralatrexate (Folotyn) for treatment of T-cell lymphoma. Sponsors withdrew their market application for 4 indications, including dinutuximab (Unituxin) for treatment of neuroblastoma was withdrawn due to the inability to supply the drug in sufficient quantities for meeting the demands and omacetaxine (Synribo) for treatment of myelogenous leukemia because of inability to address the issues identified by the EMA within the timeframe allowed.[13]

Among the 101 cancer indications that were designated with orphan drug status by the FDA and also approved by the EMA, 46 were approved for first-line therapy while 55 were indicated for second-, third-, or fourth-line therapy. Forty-five were approved for supplementary (extended) indications of already-approved drugs. There was a substantial increase in designations over time. In the US, 2 approved cancer drug indications were designated with orphan status in 2008, while 16 were approved in 2016 (**Figure 1**).

Eighty of the 101 approved cancer drug indications were first approved in the US, while market approval first took place by the EMA for the other 21. In 81% (65/80), approval in one jurisdiction followed less than a year after market authorization in the other jurisdiction.

US vs. EU differences in applying the rare disease drug designation

Among the 101 orphan designated approved cancer conditions, 33% (33/101) were approved for biomarker-derived oncologic drugs in the US, such as nivolumab (Opdivo) for the treatment of BRAF V600 mutated melanoma, or ceritinib (Zykadia) for the treatment of ALK+ non-small cell lung cancer (NSCLC), afatinib (Gilotrif) for EGFR mutated NSCLC and osimertinib (Tagrisso) for EGFR mutated NSCLC. The number of approved biomarker-defined indications with orphan designation has increased over the past years in the US. Only one biomarker-derived cancer indication was approved with orphan drug designation in 2008, while 8 were approved with orphan status in 2017. By contrast, only 9% (9/101) of approved cancer drug indications by the EMA were orphan designated biomarker-derived oncologic drugs. For example, afatinib (Gilotrif) and osimertinib (Tagrisso) got approval in both, the US and the EU, however, they only got orphan designation in the US.

Only 41 of the 101 cancer indications with orphan designation by the FDA were also designated orphan drug status at the time of market approval by the EMA. While most of the 60 remaining products never received a rare disease drug designation in the EU, 4 drugs had their orphan drug designations withdrawn by the EMA or the sponsor, including olaparib (Lynparza) for treatment of primary peritoneal cancer and later treatment of ovarian cancer and fallopian tube cancer, as well as bosutinib (Bosulif) for treatment of chronic myelogenous leukemia.

The approved cancer drug indications can be differentiated into solid and non-solid tumors. The majority (77/60, 78%) of approved cancer drugs that were only approved in the US with orphan status were indicated for solid tumors, while 22% (13/60) of approved cancer drugs had indications for non-solid tumors. Most frequently approved indications with orphan drug designation for solid tumors were melanoma (13 indications) followed by non-small cell lung cancer (11 indications), gastrointestinal cancer (5 indications), ovarian cancer (3 indications), fallopian tube cancer (3 indications), and peritoneal cancer (3 indications). Most approved cancer indications with orphan designation for non-solid tumors by the FDA were chronic myelogenous lymphoma (3 indications), multiple myeloma (2 indications), Hodgkin lymphoma (2 indications), chronic lymphocytic lymphoma (2 indications), and acute lymphocytic lymphoma (2 indications) (**Figure 2**).

By contrast, out of those approved cancer drugs that were designated with orphan status by both the FDA and the EMA, 20% (8/41) were indicated for solid tumors, and 80% (33/41) for non-solid tumors. Thyroid cancer (3 indications), ovarian cancer (2 indications), and soft tissue sarcoma (2 indications) were the most frequent solid tumors approved in both jurisdictions with orphan drug status. For non-solid tumors, multiple myeloma (8 indications), chronic lymphocytic lymphoma (8 indications) and acute lymphocytic lymphoma (4 indications) were the most frequently approved cancer drug indications with orphan designation (**Figure 3**).

Discussion

Principal findings

This review of cancer drugs newly approved with Orphan Drug Act designations by the FDA from 2008 through 2017 reveals important differences with respect to their approvals by the EMA. Less than 50% of cancer drugs with orphan designation by the FDA received orphan status in the EMA. Moreover, drugs that targeted biomarker-defined subsets of common cancer types were more frequently designated orphan status in the US than in the EU.

The number of drugs targeting subpopulations of specific cancers has increased over the last decade.[14, 15, 16, 17] Recent orphan-designated FDA-approved drugs for cancer target biomarker-defined subsets of common cancer types, such as melanoma or non-small cell lung cancer. For example, alectinib (Alecensa) and ceritinib (Zykadia) treat ALK+ non-small cell lung cancer, while crizotinib (Xalkori) targets ROS1-positive non-small cell lung cancer, and dabrafenib (Tafinlar) treats BRAF V600E mutated metastatic melanoma.[14, 18] However, none of these drugs were designated with orphan status by the EMA. In sum, our study shows, that in contrast to the US, fewer biomarker-defined cancer drugs, especially for subsets of more common diseases were designated with orphan status by the EMA (see **Figure 3** and **Appendix**). Drugs receiving designations in both settings were more likely to focus on truly rare cancers, such as multiple myeloma or follicular lymphoma. In the EU, the use of biomarkers to identify a subset of patients for whom the drug can be used appears to generally not be accepted as a basis for receiving an orphan designation.[19, 20] However, biomarker-derived cancer drugs can still get orphan status in the EU if, among other things, it is unlikely that marketing of the drug would generate sufficient returns to justify the investment needed for its development and the sponsor provides scientific evidence that the activity of the product would not be shown in the larger population.[21]

Implication for policy makers

The demonstration of "significant benefit" is mandatory for drugs to be designated with orphan status by the EMA compared to those drugs already on the market targeting the same disease.[22] "Significant benefit" means that a drug has a clinically relevant advantage or makes a major contribution to patients' care, compared with existing drugs already on the market that target the same condition.[19, 23] Significant benefit is a higher standard than the positive benefit-risk assessment that must be demonstrated by the sponsor in the marketing approval process, which does not involve an obligation to show that such a drug is more beneficial than all other methods for treating the same condition.[19] Significant benefit is required at the time of orphan designation, when it can be supported by preclinical studies, and at the time of marketing approval, when clinical data are needed.[22] Our study has shown that a few drugs had their orphan drug designations withdrawn during the marketing approval process, including olaparib (Lynparza) for treatment of primary peritoneal cancer, ovarian cancer, and fallopian tube cancer, and bosutinib (Bosulif) for treatment of chronic myelogenous leukemia. Adding a prerequisite of "significant benefit" to maintain orphan drug designation at the time of FDA approval in the US could help prevent non-first-in-class drugs targeting rare diseases from earning the same incentives as a presumptively more clinically important first-in-class drug for a

rare disease. If the second-to-market product offered significant benefits over available treatments, it would get to keep its designation.

Weaknesses of this study

This study has certain limitations. It was restricted to cancer drugs, and so is not generalizable to other drug classes. Also, we did not investigate whether all approved cancer drugs with orphan designation by the EMA between those same years also received orphan status by the FDA. Therefore, it may be possible that certain cancer drugs with orphan designation by the EMA did not get orphan designation by the FDA.

Conclusion

Orphan drug designation was intended to encourage drug development for rare conditions with unmet medical needs. We found that the FDA approves more drugs with orphan designations for cancer subgroups compared to the EMA. The statute could be revised to ensure it applies to truly rare diseases for which research investment is limited. Other changes to the US Orphan Drug Act could include assessing whether there is "significant benefit" at the time of approval if treatments already exist for a disease targeted by a new drug. Implementation of these reforms could help to improve the development of innovative cancer drugs and avoid wasting resources that might be better focused on rare cancers that lack effective treatments.

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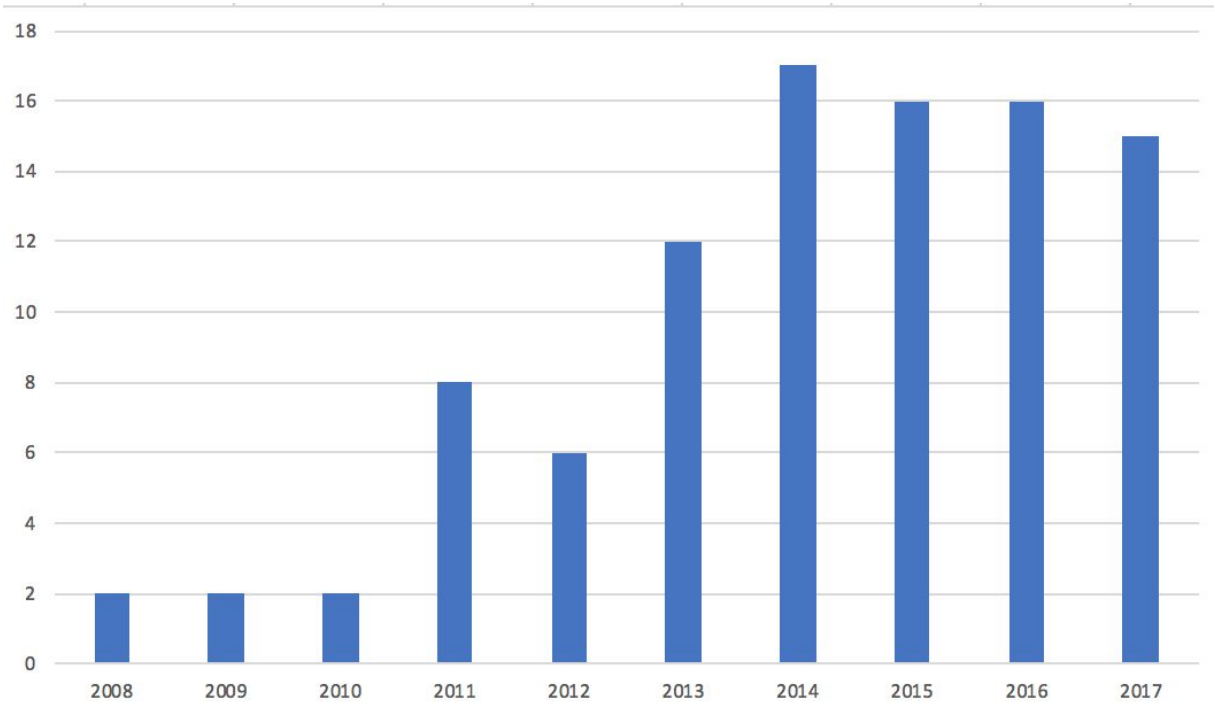
Figure 1. Approved cancer drug indications with orphan designation by the FDA from 2008 through 2017 also approved by the EMA (N=101).

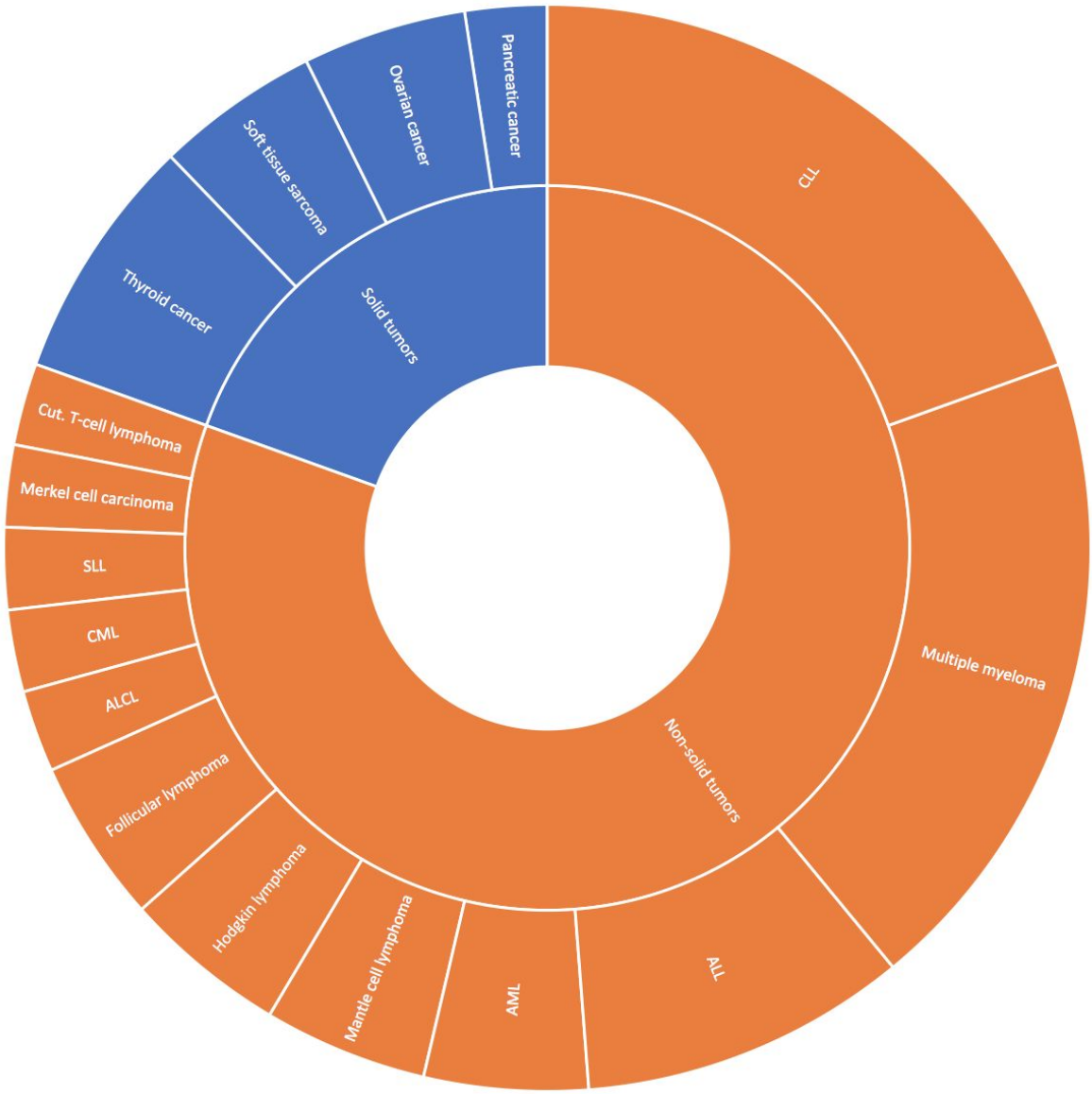


X-axis: year of marketing approval by the FDA; y-axis: number of approved cancer indications with orphan drug designation by the FDA.

Figure 2. Approved solid and non-solid tumor cancer drug indications with orphan designation only by the FDA.

ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; NSCLC = non-small cell lung cancer.

Figure 3. Approved solid and non-solid tumor cancer drug indications with orphan designation by both the FDA and the EMA.



ALCL = anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; AML = acute myeloid lymphoma; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; SLL = small lymphocytic lymphoma; cut. T-cell lymphoma = Cutaneous T-cell lymphoma.

	Cancer Drug Indications with Orphan Designation by the FDA (2008 - 2017) and Comparison with the EMA					
	FDA				**EMA**	
	Generic Name	**Trade Name**	**Marketing Approval Date**	**Designation**	**Orphan drug Status**	**Approval Date**
1	**nivolumab**	Opdivo	12/20/2017	Treatment of Stage IIb to IV melanoma	no	06/28/2018
2	**bosutinib**	Bosulif	12/19/2017	Treatment of chronic myelogenous leukemia	no	04/23/2018
3	**obinutuzumab**	Gazyva	11/16/2017	Treatment of follicular lymphoma	yes	09/18/2017
4	**Brentuximab vedotin**	Adcetris	11/09/2017	Treatment of primary cutaneous CD30-positive T-cell lymphoproliferative disorders	yes	12/15/2017
5	**dasatinib**	Sprycel	11/09/2017	Treatment of chronic myelogenous leukemia	no	07/02/2018
6	**alectinib**	Alecensa	11/06/2017	Treatment of ALK-positive non-small cell lung cancer	no	12/18/2017
7	**acalabrutinib**	Calquence	10/31/2017	Treatment of mantle cell lymphoma	no approval	
8	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of follicular lymphoma	no approval	
9	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of diffuse large B-cell lymphoma	no approval	
10	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of primary mediastinal B-cell lymphoma	no approval	
11	**pembrolizumab**	Keytruda	09/22/2017	Treatment of gastric cancer, including gastroesophageal junction adenocarcinoma	no approval	
12	**nivolumab**	Opdivo	09/22/2017	Treatment of hepatocellular carcinoma	no approval	
13	**copanlisib**	Aliqopa	09/14/2017	Treatment of follicular lymphoma	no approval	
14	**Gemtuzumab ozogamicin**	Mylotarg	09/01/2017	Treatment of acute myeloid leukemia	yes	04/19/2018
15	**Tisagenlecleucel**	Kymriah	08/30/2017	For the treatment of Acute Lymphoblastic Leukemia	no approval	

16	**inotuzumab ozogamicin**	Besponsa	08/17/2017	Treatment of B-cell acute lymphoblastic leukemia	yes	06/29/2017
17	**olaparib**	Lynparza	08/17/2017	Treatment of primary peritoneal cancer	no	12/16/2014
18	**olaparib**	Lynparza	08/17/2017	Treatment of ovarian cancer	no	12/16/2014
19	**olaparib**	Lynparza	08/17/2017	Treatment of Fallopian Tube Cancer	no	12/16/2014
20	**Cytarabine:daunorubicin liposome injection**	Vyxeos	08/03/2017	Treatment of acute myeloid leukemia	no approval	
21	**enasidenib**	Idhifa	08/01/2017	Treatment of acute myelogenous leukemia	no approval	
22	**ipilimumab**	Yervoy	07/21/2017	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no	05/31/2018
23	**daratumumab**	Darzalex	06/16/2017	Treatment of multiple myeloma	no approval	
24	**ceritinib**	Zykadia	05/26/2017	Treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase(ALK)-positive	no	06/23/2017
25	**brigatinib**	Alunbrig	04/28/2017	Treatment of anaplastic lymphoma kinase-positive (ALK+), c-ros 1 oncogene positive (ROS1+), or epidermal growth factor receptor positive (EGFR+) non-small cell lung cancer (NSCLC).	no approval	
26	**midostaurin**	Rydapt	04/28/2017	Treatment of acute myeloid leukemia	yes	09/18/2017
27	**regorafenib**	Stivarga	04/27/2017	Treatment of hepatocellular carcinoma	no	08/02/2017
28	**nivolumab**	Opdivo	04/25/2017	Treatment of Hodgkin lymphoma	no approval	
29	**methotrexate oral solution**	Xatmep	04/25/2017	Treatment of acute lymphoblastic leukemia in pediatric patients (0 through 16 years of age)	no	03/29/2017
30	**niraparib**	Zejula	03/27/2017	Treatment of ovarian cancer	yes	11/16/2017
31	**avelumab**	Bavencio	03/23/2017	Treatment of merkel cell carcinoma.	yes	09/18/2017
32	**pembrolizumab**	Keytruda	03/14/2017	Treatment of Hodgkin lymphoma	no	05/02/2017

33	**lenalidomide**	Revlimid	02/22/2017	Treatment of multiple myeloma	yes	02/23/2017
34	**ibrutinib**	Imbruvica	01/18/2017	Treatment of patients with extranodal marginal zone lymphoma (mucosa associated lymphoid tissue [MALT type] lymphoma)	no approval	
35	**ibrutinib**	Imbruvica	01/18/2017	Treatment of splenic marginal zone lymphoma	no approval	
36	**ibrutinib**	Imbruvica	01/18/2017	Treatment of nodal marginal zone lymphoma	no approval	
37	**rucaparib**	Rubraca	12/19/2016	Treatment of ovarian cancer	yes	05/24/2018
38	**bevacizumab**	Avastin	12/06/2016	Therapeutic treatment of patients with ovarian cancer	no	02/06/2017
39	**bevacizumab**	Avastin	12/06/2016	Treatment of fallopian tube carcinoma	no	02/06/2017
40	**bevacizumab**	Avastin	12/06/2016	Treatment of primary peritoneal carcinoma.	no	02/06/2017
41	**daratumumab**	Darzalex	11/21/2016	Treatment of multiple myeloma	yes	04/28/2017
42	**olaratumab**	Lartruvo	10/19/2016	Treatment of soft tissue sarcoma	yes	11/09/2016
43	**nivolumab**	Opdivo	05/17/2016	Treatment of Hodgkin lymphoma	no	06/19/2015
44	**ibrutinib**	Imbruvica	05/06/2016	Treatment of small lymphocytic lymphoma	yes	06/26/2016
45	**afatinib**	Gilotrif	04/15/2016	Treatment of non-small cell lung cancer with squamous histology.	no	03/31/2016
46	**venetoclax**	Venclexta	04/11/2016	Treatment of chronic lymphocytic leukemia	yes	12/05/2016
47	**crizotinib**	Xalkori	03/11/2016	Treatment of ALK-positive, MET-positive, or ROS-positive non-small cell lung cancer	no	08/25/2016
48	**ibrutinib**	Imbruvica	03/04/2016	Treatment of chronic lymphocytic leukemia (CLL)	yes	05/26/2016
49	**everolimus**	Afinitor	02/26/2016	Treatment of neuroendocrine tumors of gastroinstestinal or lung origin	no	05/26/2016
50	**obinutuzumab**	Gazyva	02/26/2016	Treatment of follicular lymphoma	yes	06/13/2016

51	**eribulin mesylate**	Halaven	01/28/2016	Treatment of soft tissue sarcoma	no	05/02/2016
52	**ofatumumab**	Arzerra	01/19/2016	Treatment of chronic lymphocytic leukemia	yes	12/08/2016
53	**pembrolizumab**	Keytruda	12/18/2015	Treatment of Stage IIB through IV malignant melanoma	no	07/17/2015
54	**alectinib**	Alecensa	12/11/2015	Treatment of ALK-positive non-small cell lung cancer	no	02/16/2017
55	**bendamustine for 50ml admixture**	Bendeka	12/07/2015	Treatment of Follicular Lymphoma, Small Lymphocytic Lymphoma, Lymphoplasmacytic Lymphoma, Splenic Marginal Zone Lymphoma, Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoma Tissue (MALT), and Nodal Marginal Zone Lymphoma (Collectively Indolent B-cell Non-Hodgkin's Lymphoma)	no approval	
56	**bendamustine for 50 ml admixture**	Bendeka	12/07/2015	Treatment of chronic lymphocytic leukemia	no approval	
57	**elotuzumab**	Empliciti	11/30/2015	Treatment of multiple myeloma	no	05/11/2016
58	**necitumumab**	n/a	11/24/2015	Treatment of squamous non-small cell lung cancer	no	02/15/2016
59	**ixazomib citrate**	Ninlaro	11/20/2015	Treatment of multiple myeloma	yes	11/21/2016
60	**daratumumab**	Darzalex	11/16/2015	Treatment of multiple myeloma	yes	05/20/2016
61	**osimertinib**	Tagrisso	11/13/2015	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	no	02/02/2016
62	**cobimetinib**	Cotellic	11/10/2015	Treatment of stage IIb, IIc, III, and IV melanoma with BRAFV600 mutation	no	11/20/2015
63	**ipilimumab**	Yervoy	10/28/2015	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no approval	
64	**talimogene laherparepvec**	Imlygic	10/27/2015	Treatment of stage IIb-stage IV melanoma	no	12/16/2015
65	**trabectedin**	Yondelis	10/23/2015	Treatment of soft tissue sarcoma	yes	09/17/2007

66	**irinotecan liposome injection**	n/a	10/22/2015	Treatment of pancreatic cancer	yes	10/14/2016
67	**brentuximab vedotin**	Adcetris	08/17/2015	Treatment of Hodgkin's lymphoma	yes	06/24/2016
68	**gefitinib**	Iressa	07/13/2015	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	no	06/24/2009
69	**dinutuximab**	Unituxin	03/10/2015	Treatment of neuroblastoma	withdrawal	08/14/2015
70	**panobinostat**	Farydak	02/23/2015	Treatment of multiple myeloma	yes	08/28/2015
71	**lenalidomide**	Revlimid	02/17/2015	Treatment of multiple myeloma	yes	02/19/2015
72	**lenvatinib**	Lenvima	02/13/2015	Treatment of follicullar, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer	yes	05/28/2015
73	**nivolumab**	Opdivo	12/22/2014	Treatment of Stage IIb to IV melanoma	no approval	
74	**olaparib**	Lynparza	12/19/2014	Treatment of ovarian cancer	no	12/16/2014
75	**lanreotide acetate**	Somatuline Depot	12/16/2014	Treatment of neuroendocrine tumors	no approval	
76	**blinatumomab**	Blincyto	12/03/2014	Treatment of acute lymphocytic leukemia	yes	11/23/2015
77	**bevacizumab**	Avastin	11/14/2014	Treatment of fallopian tube carcinoma	no	07/31/2014
78	**bevacizumab**	Avastin	11/14/2014	Treatment of primary peritoneal carcinoma.	no	07/31/2014
79	**bevacizumab**	Avastin	11/14/2014	Therapeutic treatment of patients with ovarian cancer	no	07/31/2014
80	**ramucirumab**	Cyramza	11/05/2014	Treatment of gastric cancer	no	12/19/2014
81	**bortezomib**	Velcade	10/08/2014	Treatment of mantle cell lymphoma.	no	01/30/2015
82	**pembrolizumab**	Keytruda	09/04/2014	Treatment of Stage IIB through IV malignant melanoma	no	07/17/2015
83	**ibrutinib**	Imbruvica	07/28/2014	Treatment of chronic lymphocytic leukemia (CLL)	yes	05/26/2016

84	**idelalisib**	Zydelig	07/23/2014	Treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma	no	09/18/2014
85	**idelalisib**	Zydelig	07/23/2014	Treatment of follicular lymphoma	no	09/18/2014
86	**Belinostat**	Beleodaq	07/03/2014	Treatment of peripheral T-cell lymphoma (PTCL)	not yet approved	
87	**ceritinib**	Zykadia	04/29/2014	Treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase(ALK)-positive	no	05/06/2015
88	**mercaptopurine oral solution**	Purixan	04/28/2014	Treatment of acute lymphoblastic leukemia in pediatric patients	yes	03/09/2012
89	**ramucirumab**	Cyramza	04/21/2014	Treatment of gastric cancer	no	12/19/2014
90	**ofatumumab**	Arzerra	04/17/2014	Treatment of chronic lymphocytic leukemia	yes	06/30/2014
91	**ibrutinib**	Imbruvica	02/12/2014	Treatment of chronic lymphocytic leukemia (CLL)	yes	10/21/2014
92	**trametinib and dabrafenib**	Mekinist And Tafinlar	01/09/2014	Treatment of Stage IIb through IV melanoma.	no	08/25/2015
93	**sorafenib**	Nexavar	11/22/2013	Treatment of medullary thyroid cancer, anaplastic thyroid cancer, and recurrent or metastatic follicular or papillary thyroid cancer	yes	05/23/2014
94	**ibrutinib**	Imbruvica	11/13/2013	Treatment of mantle cell lymphoma	yes	10/21/2014
95	**obinutuzumab**	Gazyva	11/01/2013	Treatment of chronic lymphocytic leukemia	yes	07/23/2014
96	**paclitaxel protein-bound particles**	Abraxane	09/06/2013	Treatment of pancreatic cancer.	no	12/02/2013
97	**afatinib**	Gilotrif	07/12/2013	Treatment of epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC).	no	09/25/2013
98	**denosumab**	Xgeva	06/13/2013	Treatment of patients with giant cell tumor of bone	no	09/01/2014
99	**lenalidomide**	Revlimid	06/05/2013	Treatment of mantle cell lymphoma	yes	07/08/2016
100	**trametinib**	Mekinist	05/29/2013	Treatment of Stage IIb through Stage IV melanoma	no	06/30/2014

101	**dabrafenib**	Tafinlar	05/29/2013	Treatment BRAF V600 mutation positive Stage IIB through IV melanoma	no	08/26/2013
102	**regorafenib**	Stivarga	02/25/2013	Treatment gastrointestinal stromal tumors	no	07/28/2014
103	**pomalidomide**	Pomalyst	02/08/2013	Treatment of multiple myeloma	yes	08/05/2013
104	**imatinib**	Gleevec	01/25/2013	Treatment of Philadelphia-positive acute lymphoblastic leukemia	no	06/27/2013
105	**ponatinib**	Iclusig	12/14/2012	Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL)	yes	7/01/2013
106	**ponatinib**	Iclusig	12/14/2012	Treatment of chronic myeloid leukemia	yes	07/01/2013
107	**cabozantinib**	Cometriq	11/29/2012	Treatment of follicular, medullary and anaplastic thyroid carcinoma and metastatic or locally advanced papillary thyroid cancer.	yes	03/21/2014
108	**omacetaxine mepesuccinate**	Synribo	10/26/2012	Treatment of chronic myelogenous leukemia	withdrawal	
109	**bosutinib**	Bosulif	09/04/2012	Treatment of chronic myelogenous leukemia	no	02/22/2018
110	**vinCRIStine sulfate LIPOSOME injection**	Marqibo	08/09/2012	Treatment of acute lymphoblastic leukemia	no approval	
111	**carfilzomib**	Kyprolis	07/20/2012	Treatment of multiple myeloma	yes	11/19/2015
112	**pazopanib**	Votrient	04/26/2012	Treatment of soft tissue sarcomas	no	08/03/2012
113	**Erwinia L-asparaginase**	Erwinase	11/18/2011	Treatment of acute lymphocytic leukemia.	no approval	
114	**brentuximab vedotin**	Adcetris	08/19/2011	Treatment of Hodgkin's lymphoma	yes	06/24/2016
115	**brentuximab vedotin**	Adcetris	08/19/2011	Treatment of anaplastic large cell lymphoma	yes	10/25/2012
116	**vemurafenib**	Zelboraf	08/17/2011	Treatment of patients with IIb to Stage IV melanoma positive for the BRAF(v600) mutation	no	02/17/2012
117	**romidepsin**	Istodax	06/16/2011	Treatment of non-Hodgkin T-cell lymphomas	refusal	02/12/2013

118	**everolimus**	Afinitor	05/05/2011	Treatment of neuroendocrine tumors of pancreatic origin	no	08/24/2011
119	**levoleucovorin**	Fusilev	04/29/2011	For use in combination chemotherapy with the approved agent 5-fluorouracil in the palliative treatment of metastatic adenocarcinoma of the colon and rectum	withdrawal	
120	**vandetanib**	Caprelsa(R)	04/06/2011	Treatment of patients with follicular thyroid carcinoma, medullary thyroid carcinoma, anaplastic thyroid carcinoma, and locally advanced and metastatic papillary thyroid carcinoma	no	02/17/2012
121	**peginterferon alfa-2b**	Sylatron	03/29/2011	Treatment of malignant melanoma stages IIb through IV.	no	03/09/2010
122	**ipilimumab**	Yervoy	03/25/2011	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no	07/13/2011
123	**crizotinib**	Xalkori	03/11/2011	Treatment of ALK-positive, MET-positive, or ROS-positive non-small cell lung cancer	no	10/23/2012
124	**trastuzumab**	Herceptin	10/20/2010	Treatment of HER2-overexpressing advanced adenocarcinoma of the stomach, including gastroesophageal junction	no	01/19/2010
125	**rituximab**	Rituxan	02/18/2010	Treatment of chronic lymphocytic leukemia	no	06/15/2017
126	**ofatumumab**	Arzerra	10/26/2009	Treatment of chronic lymphocytic leukemia	yes	04/19/2010
127	**pralatrexate**	Folotyn	09/25/2009	Treatment of T-cell lymphoma	refusal	06/21/2012
128	**bevacizumab**	Avastin	07/31/2009	Treatment of renal cell carcinoma	no	01/12/2005
129	**bevacizumab**	Avastin	05/05/2009	Treatment of malignant glioma	not approved	
130	**imatinib mesylate**	Gleevec	12/19/2008	Treatment of gastrointestinal stromal tumors	no	04/29/2009
131	**Fludarabine phosphate oral tablets**	n/a	12/18/2008	Treatment of B-cell chronic lymphocytic leukemia	approved decentralized system (national level)	

132	**bendamustine hydrochloride**	Treanda	10/31/2008	Treatment of Follicular Lymphoma, Small Lymphocytic Lymphoma, Lymphoplasmacytic Lymphoma, Splenic Marginal Zone Lymphoma, Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoma Tissue (MALT), and Nodal Marginal Zone Lymphoma (Collectively Indolent B-cell Non-Hodgkin's Lymphoma)	approved decentralized system (national level)	
133	**bortezomib**	Velcade	06/20/2008	Treatment of multiple myeloma	no	08/29/2008
134	**Bendamustine hydrochloride**	Treanda	03/20/2008	Treatment of chronic lymphocytic leukemia	approved decentralized system (national level)	
135	**Levoleucovorin**	Fusilev	03/07/2008	For use in conjunction with high-dose methotrexate in the treatment of osteosarcoma.	withdrawal	

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3, 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3, 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*3, 4*
Bias	9	Describe any efforts to address potential sources of bias	3-5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3-5
		(*b*) Describe any methods used to examine subgroups and interactions	3-5
		(*c*) Explain how missing data were addressed	3-5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	135 drugs
		(b) Give reasons for non-participation at each stage	3
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3
		(b) Indicate number of participants with missing data for each variable of interest	3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*3*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	4-6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5-6
Generalisability	21	Discuss the generalisability (external validity) of the study results	5-6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Application of Orphan Drug Designation to Cancer Treatments (2008 – 2017): A Comprehensive and Comparative Analysis of the US and EU

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Application of Orphan Drug Designation to Cancer Treatments (2008 – 2017): A Comprehensive and Comparative Analysis of the US and EU

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Drafting of the manuscript: Vokinger
Critical revision of the manuscript: Kesselheim
Supervision: Kesselheim
Guarantor: Vokinger

Transparency declaration: Dr. Vokinger affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Data sharing: Data are available upon request.

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Abstract

Objective: To determine differences in the characteristics of cancer drugs designated as orphan drugs by the FDA and EMA.

Design and setting: Identification of all cancer drugs (initial or supplementary indication) with orphan status approved by the FDA between 2008-2017 based on publicly accessible reports. The European public assessment reports (EPAR) was searched to determine whether these FDA-approved drugs were also approved by the EMA.

Main outcome measures: Extraction of active ingredient, trade name, approval date, and approved indication from two FDA data sources (Orphan Drug Product Designation Database, Drugs@FDA) and comparison with the same data from EPAR.

Results: The FDA approved 135 cancer drugs with Orphan Drug Act indications that met our inclusion criteria, of which 101 (75%) were also approved by the EMA. 80/101 (79%) were first approved in the US. Only 41/101 (41%) also received special rare disease designation by the EMA. 33/101 (33%) were approved for biomarker-based indications in the US, however, only 9 approved cancer drug indications by the EMA were biomarker-derived drugs. 78% (47/60) of approved cancer drugs that were only approved in the US with Orphan Drug Act status were indicated for solid tumors, 22% (13/60) had indications for non-solid tumors. By contrast, out of those approved cancer drugs that received the rare disease designation by both agencies, 20% (8/41) were indicated for solid, and 80% (33/41) for non-solid tumors.

Conclusions: The Orphan Drug Act designation was intended to encourage drug development for rare conditions. This study shows that the FDA approves more cancer drugs with such designations compared to the EMA, especially for subgroups of more prevalent cancers. One reason for the difference could be that the EU requires demonstration of significant benefit for drugs that target the same indication as a drug already on the market to earn the orphan designation.

Strengths and Limitations of this Study

Strengths:

- Our methodological and comparative approach (empirical analysis, health policy, comparative health law) enables to find possible solutions of how the US could adopt useful policies applied in the EU and thus improve the development of innovative cancer drugs.
- The inclusion of approved cancer drugs designated with Orphan Drug Act status over a time period of 10 years enables to detect informative trends in the specific jurisdiction (US and EU) as well as meaningful comparisons between the jurisdictions.
- To date, no study analyzed the differences in the application of Orphan Drug Act status on cancer drugs by the FDA and EMA.

Limitations:

- Our study is restricted to cancer drugs, and so is not generalizable to other drug classes.
- We did not investigate whether all approved cancer drugs with Orphan Drug Act designation by the EMA between those same years also received this status by the FDA. Therefore, it may be possible that certain cancer drugs with Orphan Drug Act designation by the EMA did not get this designation by the FDA.

Introduction

The US Congress passed the Orphan Drug Act in 1983 to create incentives for the development of drugs for rare diseases that might not otherwise be financially viable due to small potential patient populations.[1, 2, 3] Among other things, the statutory incentives include providing manufacturers with the opportunity to earn special tax breaks for research investment and the exclusive right to market orphan-designated drugs for 7 years from the date of marketing approval.[1, 4, 5] Such market exclusivity would allow manufacturers to charge high prices for their rare disease drug product even in the absence of patent protection and despite limited health gain.[5, 6, 7, 8, 9]

Pharmaceutical companies can apply for Orphan Drug Act designation from the Food and Drug Administration (FDA) based on either showing that the targeted condition affects fewer than 200,000 patients annually in the US, or showing no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the US, along with providing a medically plausible basis for believing that the drug would aid in the condition's treatment, prevention, or diagnosis.[10, 11]

In the European Union (EU), the European Medicines Agency (EMA) also designates drugs that target rare diseases with special status.[12] To qualify, a drug must be intended for the treatment of a disease that is life-threatening or chronically debilitating with an EU prevalence of less than 5 in 10,000, or it must be unlikely that marketing of the drug would generate sufficient returns to justify the investment needed for its development.[13, 14, 15] In addition, no satisfactory method of treatment of the condition concerned is already on the market, or, if such a method exists, the new drug must be of significant benefit to those affected by the condition.[11] Like in the US, sponsors of designated rare disease drugs in the EU earn certain incentives, including administrative regulatory fee reductions and market exclusivity.[11, 16, 15] Thus, while most prerequisites for rare disease drug designation between the US and the EU are comparable, the major difference is that the EU requires demonstration of significant benefit in case the drug targets the same indication as a drug already on the market.

Expenditure on cancer drugs dominate pharmaceutical expenditure in developed markets, with world-wide sales at $107 billion in 2015, an increase of 11.4% since 2014.[8, 17, 18] In addition, global spending on orphan-designated drugs will reach $178 billion per year by 2020, much of which will also be drugs for cancer patients.[8]

To determine whether differences in the design of the Orphan Drug Act in the US and EU lead to variations in the application of the statutory incentives, we reviewed all cancer drugs for which indications have been approved with this special status between 2008 – 2017 by the FDA and then determined whether these cancer drugs had also been approved with the same status by the EMA.

Methods

We first identified all cancer drugs with Orphan Drug Act status approved by the FDA between 1 January 2008 and 31 December 2017. The approval could have been for an initial or supplementary indication. Cancer drugs with approval for different indications were counted separately for each cancer indication. For example, bevacizumab (Avastin) was approved with Orphan Drug Act status for, among other things, treatment of patients with ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and glioblastoma. Cancer drugs with Orphan Drug Act status that were approved by the FDA for benign tumors as well as combined therapies (e.g., dabrafenib and trametinib [Mekinist]) were not included in our analysis. From two FDA data sources—the Orphan Drug Product Designation Database and Drugs@FDA—we extracted the active ingredient, trade name, orphan designation, approval date, and approved indication.

We then searched on the database of the EMA, the European public assessment reports (EPAR), to determine whether the FDA-approved cancer drugs with orphan status in our cohort were

also approved by the EMA (with or without rare disease status) as of 1 August 2018. We assumed that the same drug is available both in the EU and US if the active substance, the therapeutic indication and the Marketing Authorization Holder are the same between both territories.[19] If so, we extracted the same data as from the FDA sources. No patients were involved in this study.

Descriptive statistics were performed for the recorded variables. Trends across time and indications of cancer drugs with rare disease designation were analyzed descriptively and in comparison between the EU and US.

Patient and Public Involvement

No patients or public were involved in this study.

Results

The FDA approved 135 cancer drug indications with Orphan Drug Act designations that met our inclusion criteria. Among this sample, 101 (75%) were also approved by the EMA by 1 August 2018, including drugs with and without such a designation by the EMA (see **Appendix**). Two indications were refused market approval in the EU: romidepsin (Istodax) was refused for treatment of non-Hodgkin's lymphoma, and pralatrexate (Folotyn) for treatment of T-cell lymphoma. Sponsors withdrew their market application for 4 indications, including dinutuximab (Unituxin) for treatment of neuroblastoma was withdrawn due to the inability to supply the drug in sufficient quantities for meeting the demands and omacetaxine (Synribo) for treatment of myelogenous leukemia because of inability to address the issues identified by the EMA within the timeframe allowed.[20]

Among the 101 cancer indications that were designated with Orphan Drug Act status by the FDA and also approved by the EMA, 46 were approved for first-line therapy while 55 were indicated for second-, third-, or fourth-line therapy. Forty-five were approved for supplementary (extended) indications of already-approved drugs. There was a substantial increase in designations over time. In the US, 2 approved cancer drug indications were designated with Orphan Drug Act status in 2008, while 16 were approved in 2016 (**Figure 1**).

Eighty of the 101 approved cancer drug indications were first approved in the US, while market approval first took place by the EMA for the other 21. In 81% (65/80), approval in one jurisdiction followed less than a year after market authorization in the other jurisdiction. For example, nivolumab (Opdivo) was approved in the US in December 2017. Approval by the EMA followed less than one year later in June 2018 (see **Appendix**).

US vs. EU differences in applying the rare disease drug designation

Among the 101 Orphan Drug Act designated approved cancer conditions, 40% (40/101) were approved for biomarker-derived indications, such as nivolumab (Opdivo) for the treatment of BRAF V600 mutated melanoma, or ceritinib (Zykadia) for the treatment of ALK+ non-small cell lung cancer (NSCLC), afatinib (Gilotrif) for EGFR mutated NSCLC and osimertinib (Tagrisso) for EGFR mutated NSCLC. The number of approved biomarker-defined indications with Orphan Drug Act designation has increased over the past years in the US (**Figure 2**). Only one biomarker-derived cancer indication was approved with Orphan Drug Act designation in 2008, while 8 were approved with Orphan Drug Act status in 2017. By contrast, only 10% (10/101) of approved cancer drug indications by the EMA were rare-disease designated biomarker-defined subsets of disease. For example, afatinib (Gilotrif) and osimertinib (Tagrisso) got approval in both the US and the EU, however, they only got Orphan Drug Act designation in the US.

Only 41 of the 101 cancer indications with Orphan Drug Act designation by the FDA were also designated with rare disease status at the time of market approval by the EMA. While most of the 60 remaining products never received a rare disease drug designation in the EU, 4 drugs had their

designations withdrawn by the EMA or the sponsor, including olaparib (Lynparza) for treatment of primary peritoneal cancer and later treatment of ovarian cancer and fallopian tube cancer, as well as bosutinib (Bosulif) for treatment of chronic myelogenous leukemia.

The approved cancer drug indications can be differentiated into solid and non-solid tumors.[9, 21, 22, 23] The majority (47/60, 78%) of approved cancer drugs that were only approved in the US with Orphan Drug Act status were indicated for solid tumors, while 22% (13/60) of approved cancer drugs had indications for non-solid tumors. Most frequently approved indications with Orphan Drug Act designation for solid tumors were melanoma (13 indications) followed by non-small cell lung cancer (11 indications), gastrointestinal cancer (5 indications), ovarian cancer (3 indications), fallopian tube cancer (3 indications), and peritoneal cancer (3 indications). Most approved cancer indications with Orphan Drug Act designation for non-solid tumors by the FDA were chronic myelogenous lymphoma (3 indications), multiple myeloma (2 indications), Hodgkin lymphoma (2 indications), chronic lymphocytic lymphoma (2 indications), and acute lymphocytic lymphoma (2 indications) (**Figure 3**).

By contrast, out of those approved cancer drugs that were designated with rare disease status by both the FDA and the EMA, 20% (8/41) were indicated for solid tumors, and 80% (33/41) for non-solid tumors. Thyroid cancer (3 indications), ovarian cancer (2 indications), and soft tissue sarcoma (2 indications) were the most frequent solid tumors approved in both jurisdictions with orphan drug status. For non-solid tumors, multiple myeloma (8 indications), chronic lymphocytic lymphoma (8 indications) and acute lymphocytic lymphoma (4 indications) were the most frequently approved cancer drug indications with the rare disease designation (**Figure 4**).

Discussion

This review of cancer drugs newly approved with Orphan Drug Act designations by the FDA from 2008 through 2017 reveals important differences with respect to their approvals by the EMA. Less than 50% of cancer drugs with an Orphan Drug Act designation by the FDA received such status in the EMA. Our results are consistent with other studies showing that the US has more Orphan Drug Act designations in general and specifically for oncology drugs compared to the EU.[19, 24, 25] Drugs that targeted biomarker-defined subsets of common cancer types often received Orphan Drug Act status in the US, but did not get similar status in the EU.

The number of drugs targeting subpopulations of specific cancers has increased over the last decade with a simultaneous increase in the number of Orphan Drug Act designation by the FDA for drugs indicated for cancers defined as biomarker-based subsets of more common cancers.[26, 27, 28, 29] However, it is interesting to note that the EMA does not follow this pattern (**Figure 2**). Among the 101 orphan-designated drugs from 2008 through 2017, 40% (40/101) were approved for indications defined in part by biomarkers by the FDA, as compared to only 10% (10/101) by the EMA. For example, the FDA approved alectinib (Alecensa) and ceritinib (Zykadia) to treat ALK+ non-small cell lung cancer, crizotinib (Xalkori) to treat ROS1-positive non-small cell lung cancer, and dabrafenib (Tafinlar) to treat BRAF V600E mutated metastatic melanoma.[26, 30] However, none of these drugs were designated with rare disease status by the EMA (see **Figure 4** and **Appendix**).

Drugs receiving designations in both settings were more likely to focus on truly rare cancers, such as multiple myeloma or follicular lymphoma. In the EU, the use of biomarkers to identify a subset of patients for whom the drug can be used appears to generally not be accepted as a basis for receiving a rare disease designation.[31, 32] However, biomarker-derived cancer drugs can still get rare disease status in the EU if, among other things, it is unlikely that marketing of the drug would generate sufficient returns to justify the investment needed for its development and the sponsor provides scientific evidence that the activity of the product would not be shown in the larger population.[33]

Implication for policy makers

The demonstration of "significant benefit" is mandatory for drugs to be designated with rare disease status by the EMA compared to those drugs already on the market targeting the same disease.[15, 34] "Significant benefit" means that a drug has a clinically relevant advantage or makes a major contribution to patients' care, compared with existing drugs already on the market that target the same condition.[31, 35] Significant benefit is a higher standard than the positive benefit-risk assessment that must be demonstrated by the sponsor in the marketing approval process, which does not involve an obligation to show that such a drug is more beneficial than all other methods for treating the same condition.[19] Significant benefit is required at the time of rare disease designation, when it can be supported by preclinical studies, and at the time of marketing approval, when clinical data are needed.[34] Our study has shown that a few drugs had their orphan drug designations withdrawn during the marketing approval process, including olaparib (Lynparza) for treatment of primary peritoneal cancer, ovarian cancer, and fallopian tube cancer, and bosutinib (Bosulif) for treatment of chronic myelogenous leukemia. Adding a prerequisite of "significant benefit" to maintain Orphan Drug Act designation at the time of FDA approval in the US could help prevent non-first-in-class drugs targeting rare diseases from earning the same incentives as a presumptively more clinically important first-in-class drug for a rare disease. If the second-to-market product offered significant benefits over available treatments, it would get to keep its designation.

Weaknesses of this study

This study has certain limitations. It was restricted to cancer drugs, and so is not generalizable to other drug classes. Also, we did not investigate whether all approved cancer drugs with rare disease designation by the EMA between those same years also received Orphan Drug Act status by the FDA. Therefore, it may be possible that certain cancer drugs with rare disease designation by the EMA did not get Orphan Drug Act designation by the FDA.

Conclusion

The Orphan Drug Act in the US was intended to encourage drug development for rare conditions with unmet medical needs. We found that the FDA approves more drugs with such designations for cancer subgroups compared to the EMA. The statute could be revised to ensure it applies to truly rare diseases for which research investment is limited. Other changes to the US Orphan Drug Act could include assessing whether there is "significant benefit" at the time of approval if treatments already exist for a disease targeted by a new drug. Implementation of these reforms could help to improve the development of innovative cancer drugs and by encouraging more resources to be directed to rare cancers that lack effective treatments.

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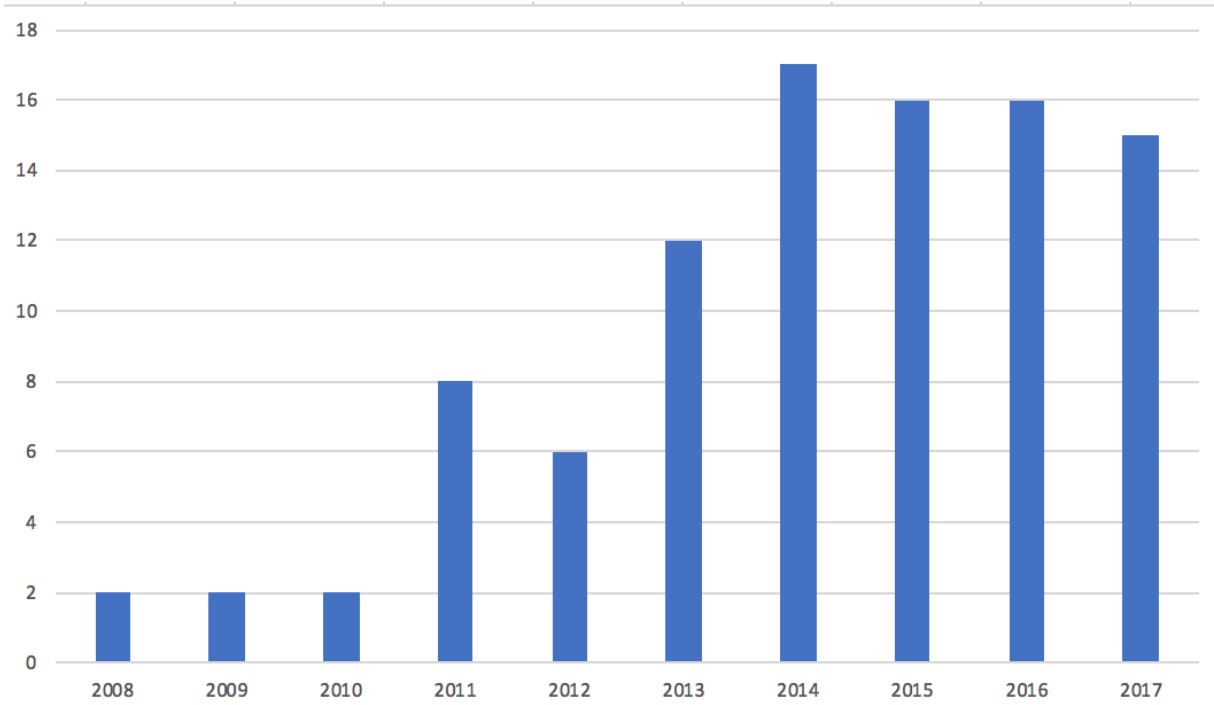
Figure 1. Approved cancer drug indications with Orphan Drug Act designation by the FDA from 2008 through 2017 that were also approved by the EMA (N=101).
X-axis: year of marketing approval by the FDA; y-axis: number of approved cancer indications with orphan drug designation by the FDA.

Figure 2. Numbers of FDA- and EMA-approved drugs indicated for biomarker-defined rare cancer indications from 2008 through 2017.
X-axis: year of marketing approval by the FDA and EMA; y-axis: number of approved biomarker-derived cancer indications with orphan drug designation; blue = Approved biomarker-derived cancer indications with orphan designation by the FDA; orange = Approved biomarker-derived cancer indications with orphan designation by the EMA.

Figure 3. FDA-approved solid and non-solid tumor cancer drug indications with Orphan Drug Act designation.
ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; NSCLC = non-small cell lung cancer.

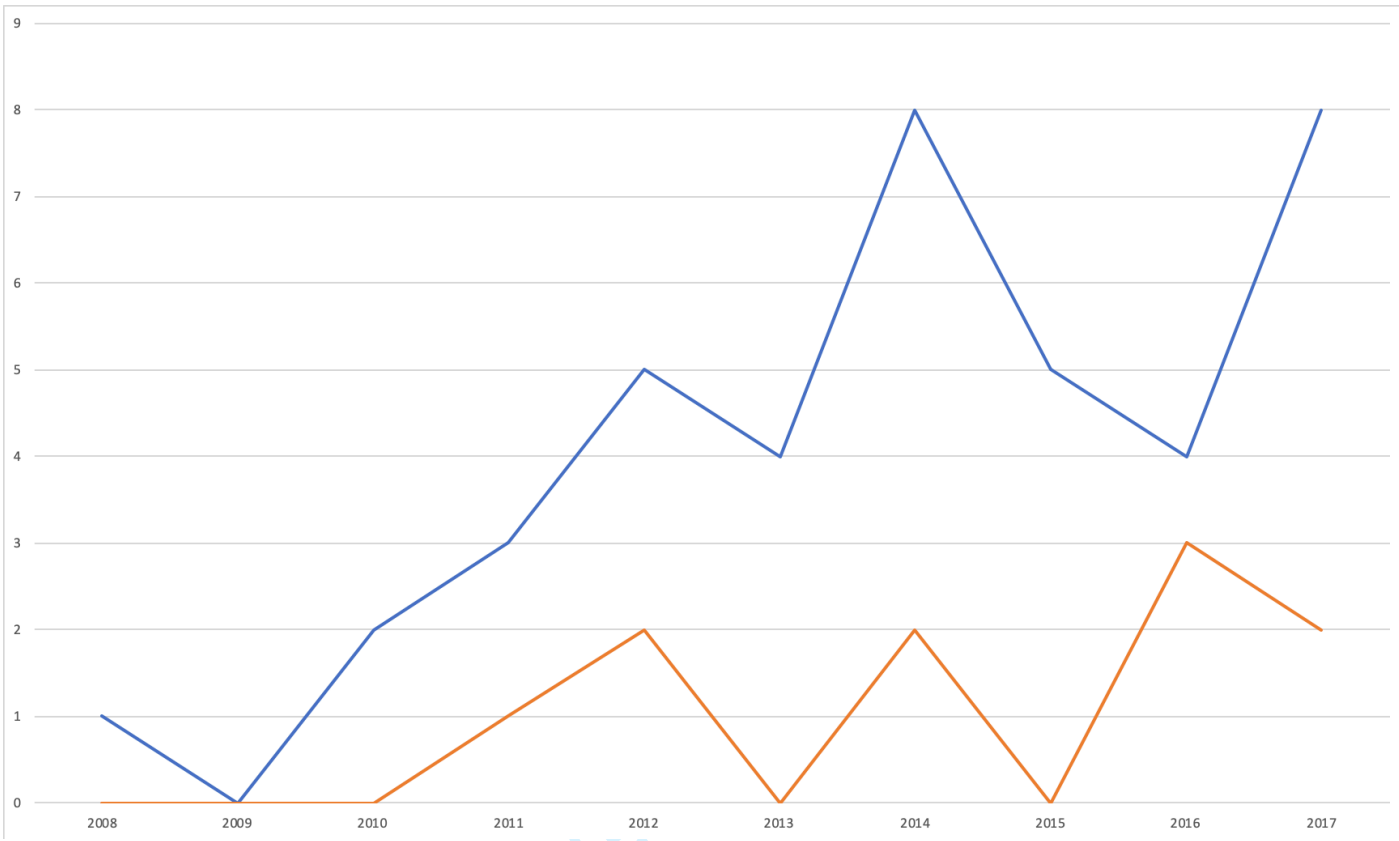
Figure 4. FDA- and EMA-approved solid and non-solid tumor cancer drug indications with Orphan Drug Act designation.
ALCL = anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; AML = acute myeloid lymphoma; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; SLL = small lymphocytic lymphoma; cut. T-cell lymphoma = Cutaneous T-cell lymphoma.

Figure 1. Approved cancer drug indications with Orphan Drug Act designation by the FDA from 2008 through 2017 that were also approved by the EMA (N=101).



X-axis: year of marketing approval by the FDA; y-axis: number of approved cancer indications with orphan drug designation by the FDA.

Figure 2. Numbers of FDA- and EMA-approved drugs indicated for biomarker-defined rare cancer indications from 2008 through 2017.



X-axis: year of marketing approval by the FDA and EMA; y-axis: number of approved biomarker-derived cancer indications with orphan drug designation; blue = Approved biomarker-derived cancer indications with orphan designation by the FDA; orange = Approved biomarker-derived cancer indications with orphan designation by the EMA.

Figure 3. FDA-approved solid and non-solid tumor cancer drug indications with Orphan Drug Act designation.

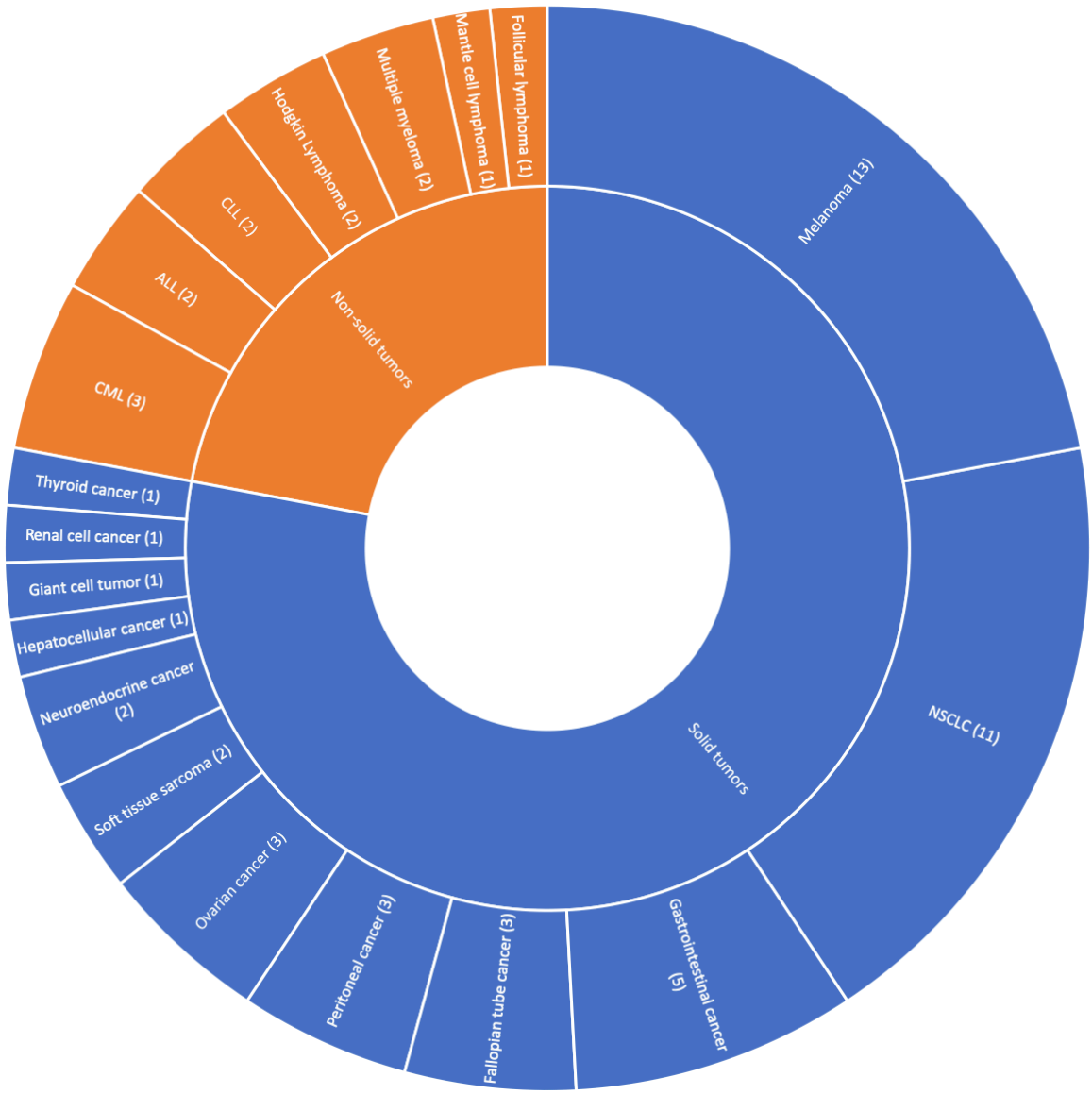


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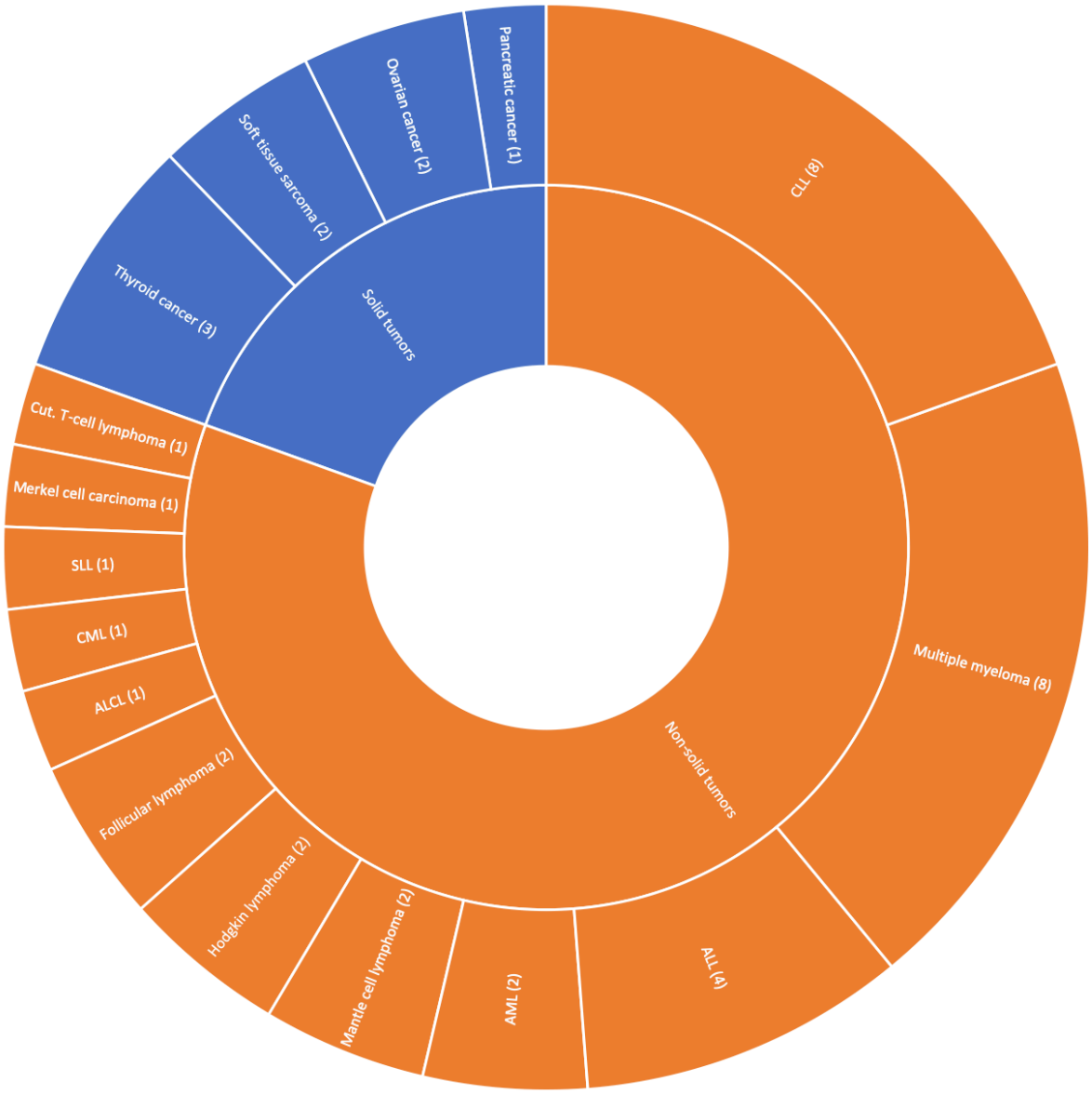
Figure 4. FDA- and EMA-approved solid and non-solid tumor cancer drug indications with Orphan Drug Act designation.



ALCL = anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; AML = acute myeloid lymphoma; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; SLL = small lymphocytic lymphoma; cut. T-cell lymphoma = Cutaneous T-cell lymphoma.

	Cancer Drug Indications with Orphan Designation by the FDA (2008 - 2017) and Comparison with the EMA					
	FDA				**EMA**	
	Generic Name	**Trade Name**	**Marketing Approval Date**	**Designation**	**Orphan drug Status**	**Approval Date**
1	**nivolumab**	Opdivo	12/20/2017	Treatment of Stage IIb to IV melanoma	no	06/28/2018
2	**bosutinib**	Bosulif	12/19/2017	Treatment of chronic myelogenous leukemia	no	04/23/2018
3	**obinutuzumab**	Gazyva	11/16/2017	Treatment of follicular lymphoma	yes	09/18/2017
4	**Brentuximab vedotin**	Adcetris	11/09/2017	Treatment of primary cutaneous CD30-positive T-cell lymphoproliferative disorders	yes	12/15/2017
5	**dasatinib**	Sprycel	11/09/2017	Treatment of chronic myelogenous leukemia	no	07/02/2018
6	**alectinib**	Alecensa	11/06/2017	Treatment of ALK-positive non-small cell lung cancer	no	12/18/2017
7	**acalabrutinib**	Calquence	10/31/2017	Treatment of mantle cell lymphoma	no approval	
8	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of follicular lymphoma	no approval	
9	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of diffuse large B-cell lymphoma	no approval	
10	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of primary mediastinal B-cell lymphoma	no approval	
11	**pembrolizumab**	Keytruda	09/22/2017	Treatment of gastric cancer, including gastroesophageal junction adenocarcinoma	no approval	
12	**nivolumab**	Opdivo	09/22/2017	Treatment of hepatocellular carcinoma	no approval	
13	**copanlisib**	Aliqopa	09/14/2017	Treatment of follicular lymphoma	no approval	
14	**Gemtuzumab ozogamicin**	Mylotarg	09/01/2017	Treatment of acute myeloid leukemia	yes	04/19/2018
15	**Tisagenlecleucel**	Kymriah	08/30/2017	For the treatment of Acute Lymphoblastic Leukemia	no approval	

16	**inotuzumab ozogamicin**	Besponsa	08/17/2017	Treatment of B-cell acute lymphoblastic leukemia	yes	06/29/2017
17	**olaparib**	Lynparza	08/17/2017	Treatment of primary peritoneal cancer	no	12/16/2014
18	**olaparib**	Lynparza	08/17/2017	Treatment of ovarian cancer	no	12/16/2014
19	**olaparib**	Lynparza	08/17/2017	Treatment of Fallopian Tube Cancer	no	12/16/2014
20	**Cytarabine:daunorubicin liposome injection**	Vyxeos	08/03/2017	Treatment of acute myeloid leukemia	no approval	
21	**enasidenib**	Idhifa	08/01/2017	Treatment of acute myelogenous leukemia	no approval	
22	**ipilimumab**	Yervoy	07/21/2017	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no	05/31/2018
23	**daratumumab**	Darzalex	06/16/2017	Treatment of multiple myeloma	no approval	
24	**ceritinib**	Zykadia	05/26/2017	Treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase(ALK)-positive	no	06/23/2017
25	**brigatinib**	Alunbrig	04/28/2017	Treatment of anaplastic lymphoma kinase-positive (ALK+), c-ros 1 oncogene positive (ROS1+), or epidermal growth factor receptor positive (EGFR+) non-small cell lung cancer (NSCLC).	no approval	
26	**midostaurin**	Rydapt	04/28/2017	Treatment of acute myeloid leukemia	yes	09/18/2017
27	**regorafenib**	Stivarga	04/27/2017	Treatment of hepatocellular carcinoma	no	08/02/2017
28	**nivolumab**	Opdivo	04/25/2017	Treatment of Hodgkin lymphoma	no approval	
29	**methotrexate oral solution**	Xatmep	04/25/2017	Treatment of acute lymphoblastic leukemia in pediatric patients (0 through 16 years of age)	no	03/29/2017
30	**niraparib**	Zejula	03/27/2017	Treatment of ovarian cancer	yes	11/16/2017
31	**avelumab**	Bavencio	03/23/2017	Treatment of merkel cell carcinoma.	yes	09/18/2017
32	**pembrolizumab**	Keytruda	03/14/2017	Treatment of Hodgkin lymphoma	no	05/02/2017

33	**lenalidomide**	Revlimid	02/22/2017	Treatment of multiple myeloma	yes	02/23/2017
34	**ibrutinib**	Imbruvica	01/18/2017	Treatment of patients with extranodal marginal zone lymphoma (mucosa associated lymphoid tissue [MALT type] lymphoma)	no approval	
35	**ibrutinib**	Imbruvica	01/18/2017	Treatment of splenic marginal zone lymphoma	no approval	
36	**ibrutinib**	Imbruvica	01/18/2017	Treatment of nodal marginal zone lymphoma	no approval	
37	**rucaparib**	Rubraca	12/19/2016	Treatment of ovarian cancer	yes	05/24/2018
38	**bevacizumab**	Avastin	12/06/2016	Therapeutic treatment of patients with ovarian cancer	no	02/06/2017
39	**bevacizumab**	Avastin	12/06/2016	Treatment of fallopian tube carcinoma	no	02/06/2017
40	**bevacizumab**	Avastin	12/06/2016	Treatment of primary peritoneal carcinoma.	no	02/06/2017
41	**daratumumab**	Darzalex	11/21/2016	Treatment of multiple myeloma	yes	04/28/2017
42	**olaratumab**	Lartruvo	10/19/2016	Treatment of soft tissue sarcoma	yes	11/09/2016
43	**nivolumab**	Opdivo	05/17/2016	Treatment of Hodgkin lymphoma	no	06/19/2015
44	**ibrutinib**	Imbruvica	05/06/2016	Treatment of small lymphocytic lymphoma	yes	06/26/2016
45	**afatinib**	Gilotrif	04/15/2016	Treatment of non-small cell lung cancer with squamous histology.	no	03/31/2016
46	**venetoclax**	Venclexta	04/11/2016	Treatment of chronic lymphocytic leukemia	yes	12/05/2016
47	**crizotinib**	Xalkori	03/11/2016	Treatment of ALK-positive, MET-positive, or ROS-positive non-small cell lung cancer	no	08/25/2016
48	**ibrutinib**	Imbruvica	03/04/2016	Treatment of chronic lymphocytic leukemia (CLL)	yes	05/26/2016
49	**everolimus**	Afinitor	02/26/2016	Treatment of neuroendocrine tumors of gastroinstestinal or lung origin	no	05/26/2016
50	**obinutuzumab**	Gazyva	02/26/2016	Treatment of follicular lymphoma	yes	06/13/2016

51	**eribulin mesylate**	Halaven	01/28/2016	Treatment of soft tissue sarcoma	no	05/02/2016
52	**ofatumumab**	Arzerra	01/19/2016	Treatment of chronic lymphocytic leukemia	yes	12/08/2016
53	**pembrolizumab**	Keytruda	12/18/2015	Treatment of Stage IIB through IV malignant melanoma	no	07/17/2015
54	**alectinib**	Alecensa	12/11/2015	Treatment of ALK-positive non-small cell lung cancer	no	02/16/2017
55	**bendamustine for 50ml admixture**	Bendeka	12/07/2015	Treatment of Follicular Lymphoma, Small Lymphocytic Lymphoma, Lymphoplasmacytic Lymphoma, Splenic Marginal Zone Lymphoma, Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoma Tissue (MALT), and Nodal Marginal Zone Lymphoma (Collectively Indolent B-cell Non-Hodgkin's Lymphoma)	no approval	
56	**bendamustine for 50 ml admixture**	Bendeka	12/07/2015	Treatment of chronic lymphocytic leukemia	no approval	
57	**elotuzumab**	Empliciti	11/30/2015	Treatment of multiple myeloma	no	05/11/2016
58	**necitumumab**	n/a	11/24/2015	Treatment of squamous non-small cell lung cancer	no	02/15/2016
59	**ixazomib citrate**	Ninlaro	11/20/2015	Treatment of multiple myeloma	yes	11/21/2016
60	**daratumumab**	Darzalex	11/16/2015	Treatment of multiple myeloma	yes	05/20/2016
61	**osimertinib**	Tagrisso	11/13/2015	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	no	02/02/2016
62	**cobimetinib**	Cotellic	11/10/2015	Treatment of stage IIb, IIc, III, and IV melanoma with BRAFV600 mutation	no	11/20/2015
63	**ipilimumab**	Yervoy	10/28/2015	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no approval	
64	**talimogene laherparepvec**	Imlygic	10/27/2015	Treatment of stage IIb-stage IV melanoma	no	12/16/2015
65	**trabectedin**	Yondelis	10/23/2015	Treatment of soft tissue sarcoma	yes	09/17/2007

66	**irinotecan liposome injection**	n/a	10/22/2015	Treatment of pancreatic cancer	yes	10/14/2016
67	**brentuximab vedotin**	Adcetris	08/17/2015	Treatment of Hodgkin's lymphoma	yes	06/24/2016
68	**gefitinib**	Iressa	07/13/2015	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	no	06/24/2009
69	**dinutuximab**	Unituxin	03/10/2015	Treatment of neuroblastoma	withdrawal	08/14/2015
70	**panobinostat**	Farydak	02/23/2015	Treatment of multiple myeloma	yes	08/28/2015
71	**lenalidomide**	Revlimid	02/17/2015	Treatment of multiple myeloma	yes	02/19/2015
72	**lenvatinib**	Lenvima	02/13/2015	Treatment of follicullar, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer	yes	05/28/2015
73	**nivolumab**	Opdivo	12/22/2014	Treatment of Stage IIb to IV melanoma	no approval	
74	**olaparib**	Lynparza	12/19/2014	Treatment of ovarian cancer	no	12/16/2014
75	**lanreotide acetate**	Somatuline Depot	12/16/2014	Treatment of neuroendocrine tumors	no approval	
76	**blinatumomab**	Blincyto	12/03/2014	Treatment of acute lymphocytic leukemia	yes	11/23/2015
77	**bevacizumab**	Avastin	11/14/2014	Treatment of fallopian tube carcinoma	no	07/31/2014
78	**bevacizumab**	Avastin	11/14/2014	Treatment of primary peritoneal carcinoma.	no	07/31/2014
79	**bevacizumab**	Avastin	11/14/2014	Therapeutic treatment of patients with ovarian cancer	no	07/31/2014
80	**ramucirumab**	Cyramza	11/05/2014	Treatment of gastric cancer	no	12/19/2014
81	**bortezomib**	Velcade	10/08/2014	Treatment of mantle cell lymphoma.	no	01/30/2015
82	**pembrolizumab**	Keytruda	09/04/2014	Treatment of Stage IIB through IV malignant melanoma	no	07/17/2015
83	**ibrutinib**	Imbruvica	07/28/2014	Treatment of chronic lymphocytic leukemia (CLL)	yes	05/26/2016

84	**idelalisib**	Zydelig	07/23/2014	Treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma	no	09/18/2014
85	**idelalisib**	Zydelig	07/23/2014	Treatment of follicular lymphoma	no	09/18/2014
86	**Belinostat**	Beleodaq	07/03/2014	Treatment of peripheral T-cell lymphoma (PTCL)	not yet approved	
87	**ceritinib**	Zykadia	04/29/2014	Treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase(ALK)-positive	no	05/06/2015
88	**mercaptopurine oral solution**	Purixan	04/28/2014	Treatment of acute lymphoblastic leukemia in pediatric patients	yes	03/09/2012
89	**ramucirumab**	Cyramza	04/21/2014	Treatment of gastric cancer	no	12/19/2014
90	**ofatumumab**	Arzerra	04/17/2014	Treatment of chronic lymphocytic leukemia	yes	06/30/2014
91	**ibrutinib**	Imbruvica	02/12/2014	Treatment of chronic lymphocytic leukemia (CLL)	yes	10/21/2014
92	**trametinib and dabrafenib**	Mekinist And Tafinlar	01/09/2014	Treatment of Stage IIb through IV melanoma.	no	08/25/2015
93	**sorafenib**	Nexavar	11/22/2013	Treatment of medullary thyroid cancer, anaplastic thyroid cancer, and recurrent or metastatic follicular or papillary thyroid cancer	yes	05/23/2014
94	**ibrutinib**	Imbruvica	11/13/2013	Treatment of mantle cell lymphoma	yes	10/21/2014
95	**obinutuzumab**	Gazyva	11/01/2013	Treatment of chronic lymphocytic leukemia	yes	07/23/2014
96	**paclitaxel protein-bound particles**	Abraxane	09/06/2013	Treatment of pancreatic cancer.	no	12/02/2013
97	**afatinib**	Gilotrif	07/12/2013	Treatment of epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC).	no	09/25/2013
98	**denosumab**	Xgeva	06/13/2013	Treatment of patients with giant cell tumor of bone	no	09/01/2014
99	**lenalidomide**	Revlimid	06/05/2013	Treatment of mantle cell lymphoma	yes	07/08/2016
100	**trametinib**	Mekinist	05/29/2013	Treatment of Stage IIb through Stage IV melanoma	no	06/30/2014

101	**dabrafenib**	Tafinlar	05/29/2013	Treatment BRAF V600 mutation positive Stage IIB through IV melanoma	no	08/26/2013
102	**regorafenib**	Stivarga	02/25/2013	Treatment gastrointestinal stromal tumors	no	07/28/2014
103	**pomalidomide**	Pomalyst	02/08/2013	Treatment of multiple myeloma	yes	08/05/2013
104	**imatinib**	Gleevec	01/25/2013	Treatment of Philadelphia-positive acute lymphoblastic leukemia	no	06/27/2013
105	**ponatinib**	Iclusig	12/14/2012	Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL)	yes	7/01/2013
106	**ponatinib**	Iclusig	12/14/2012	Treatment of chronic myeloid leukemia	yes	07/01/2013
107	**cabozantinib**	Cometriq	11/29/2012	Treatment of follicular, medullary and anaplastic thyroid carcinoma and metastatic or locally advanced papillary thyroid cancer.	yes	03/21/2014
108	**omacetaxine mepesuccinate**	Synribo	10/26/2012	Treatment of chronic myelogenous leukemia	withdrawal	
109	**bosutinib**	Bosulif	09/04/2012	Treatment of chronic myelogenous leukemia	no	02/22/2018
110	**vinCRIStine sulfate LIPOSOME injection**	Marqibo	08/09/2012	Treatment of acute lymphoblastic leukemia	no approval	
111	**carfilzomib**	Kyprolis	07/20/2012	Treatment of multiple myeloma	yes	11/19/2015
112	**pazopanib**	Votrient	04/26/2012	Treatment of soft tissue sarcomas	no	08/03/2012
113	**Erwinia L-asparaginase**	Erwinase	11/18/2011	Treatment of acute lymphocytic leukemia.	no approval	
114	**brentuximab vedotin**	Adcetris	08/19/2011	Treatment of Hodgkin's lymphoma	yes	06/24/2016
115	**brentuximab vedotin**	Adcetris	08/19/2011	Treatment of anaplastic large cell lymphoma	yes	10/25/2012
116	**vemurafenib**	Zelboraf	08/17/2011	Treatment of patients with IIb to Stage IV melanoma positive for the BRAF(v600) mutation	no	02/17/2012
117	**romidepsin**	Istodax	06/16/2011	Treatment of non-Hodgkin T-cell lymphomas	refusal	02/12/2013

118	**everolimus**	Afinitor	05/05/2011	Treatment of neuroendocrine tumors of pancreatic origin	no	08/24/2011
119	**levoleucovorin**	Fusilev	04/29/2011	For use in combination chemotherapy with the approved agent 5-fluorouracil in the palliative treatment of metastatic adenocarcinoma of the colon and rectum	withdrawal	
120	**vandetanib**	Caprelsa(R)	04/06/2011	Treatment of patients with follicular thyroid carcinoma, medullary thyroid carcinoma, anaplastic thyroid carcinoma, and locally advanced and metastatic papillary thyroid carcinoma	no	02/17/2012
121	**peginterferon alfa-2b**	Sylatron	03/29/2011	Treatment of malignant melanoma stages IIb through IV.	no	03/09/2010
122	**ipilimumab**	Yervoy	03/25/2011	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no	07/13/2011
123	**crizotinib**	Xalkori	03/11/2011	Treatment of ALK-positive, MET-positive, or ROS-positive non-small cell lung cancer	no	10/23/2012
124	**trastuzumab**	Herceptin	10/20/2010	Treatment of HER2-overexpressing advanced adenocarcinoma of the stomach, including gastroesophageal junction	no	01/19/2010
125	**rituximab**	Rituxan	02/18/2010	Treatment of chronic lymphocytic leukemia	no	06/15/2017
126	**ofatumumab**	Arzerra	10/26/2009	Treatment of chronic lymphocytic leukemia	yes	04/19/2010
127	**pralatrexate**	Folotyn	09/25/2009	Treatment of T-cell lymphoma	refusal	06/21/2012
128	**bevacizumab**	Avastin	07/31/2009	Treatment of renal cell carcinoma	no	01/12/2005
129	**bevacizumab**	Avastin	05/05/2009	Treatment of malignant glioma	not approved	
130	**imatinib mesylate**	Gleevec	12/19/2008	Treatment of gastrointestinal stromal tumors	no	04/29/2009
131	**Fludarabine phosphate oral tablets**	n/a	12/18/2008	Treatment of B-cell chronic lymphocytic leukemia	approved decentralized system (national level)	

132	**bendamustine hydrochloride**	Treanda	10/31/2008	Treatment of Follicular Lymphoma, Small Lymphocytic Lymphoma, Lymphoplasmacytic Lymphoma, Splenic Marginal Zone Lymphoma, Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoma Tissue (MALT), and Nodal Marginal Zone Lymphoma (Collectively Indolent B-cell Non-Hodgkin's Lymphoma)	approved decentralized system (national level)	
133	**bortezomib**	Velcade	06/20/2008	Treatment of multiple myeloma	no	08/29/2008
134	**Bendamustine hydrochloride**	Treanda	03/20/2008	Treatment of chronic lymphocytic leukemia	approved decentralized system (national level)	
135	**Levoleucovorin**	Fusilev	03/07/2008	For use in conjunction with high-dose methotrexate in the treatment of osteosarcoma.	withdrawal	

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3, 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3, 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*3, 4*
Bias	9	Describe any efforts to address potential sources of bias	3-5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3-5
		(*b*) Describe any methods used to examine subgroups and interactions	3-5
		(*c*) Explain how missing data were addressed	3-5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	135 drugs
		(b) Give reasons for non-participation at each stage	3
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3
		(b) Indicate number of participants with missing data for each variable of interest	3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*3*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	4-6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5-6
Generalisability	21	Discuss the generalisability (external validity) of the study results	5-6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Application of Orphan Drug Designation to Cancer Treatments (2008 – 2017): A Comprehensive and Comparative Analysis of the US and EU

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Drafting of the manuscript: Vokinger
Critical revision of the manuscript: Kesselheim
Supervision: Kesselheim
Guarantor: Vokinger

Transparency declaration: Dr. Vokinger affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval: An ethical approval was not required for this study.

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Data sharing: Data are available upon request.

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Abstract

Objective: To determine differences in the characteristics of cancer drugs designated as orphan drugs by the FDA and EMA.

Design and setting: Identification of all cancer drugs (initial or supplementary indication) with orphan status approved by the FDA between 2008-2017 based on publicly accessible reports. The European public assessment reports (EPAR) was searched to determine whether these FDA-approved drugs were also approved by the EMA.

Main outcome measures: Extraction of active ingredient, trade name, approval date, and approved indication from two FDA data sources (Orphan Drug Product Designation Database, Drugs@FDA) and comparison with the same data from EPAR.

Results: The FDA approved 135 cancer drugs with orphan indications that met our inclusion criteria, of which 101 (75%) were also approved by the EMA. 80/101 (79%) were first approved in the US. Only 41/101 (41%) also received orphan designation by the EMA. 33/101 (33%) were approved for biomarker-based indications in the US, however, only 9 approved cancer drug indications by the EMA were biomarker-derived drugs. 78% (47/60) of approved cancer drugs that were only approved in the US with orphan status were indicated for solid tumors, 22% (13/60) had indications for non-solid tumors. By contrast, out of those approved cancer drugs that received orphan designation by both agencies, 20% (8/41) were indicated for solid, and 80% (33/41) for non-solid tumors.

Conclusions: Orphan designation was intended to encourage drug development for rare conditions. This study shows that the FDA approves more cancer drugs with such designations compared to the EMA, especially for subgroups of more prevalent cancers. One reason for the difference could be that the EU requires demonstration of significant benefit for drugs that target the same indication as a drug already on the market to earn the orphan designation.

Strengths and Limitations of this Study

Strengths:

- Our methodological and comparative approach (empirical analysis, health policy, comparative health law) enables to find possible solutions of how the US could adopt useful policies applied in the EU and thus improve the development of innovative cancer drugs.
- The inclusion of approved cancer drugs designated with orphan status over a time period of 10 years enables to detect informative trends in the specific jurisdiction (US and EU) as well as meaningful comparisons between the jurisdictions.
- To date, no study analyzed the differences in the application of orphan status on cancer drugs by the FDA and EMA.

Limitations:

- Our study is restricted to cancer drugs, and so is not generalizable to other drug classes.
- We did not investigate whether all approved cancer drugs with orphan designation by the EMA between those same years also received this status by the FDA. Therefore, it may be possible that certain cancer drugs with orphan designation by the EMA did not get this designation by the FDA.

Introduction

The US Congress passed the Orphan Drug Act in 1983 to create incentives for the development of drugs for rare diseases that might not otherwise be financially viable due to small potential patient populations.[1, 2, 3] Among other things, the statutory incentives include providing manufacturers with the opportunity to earn special tax breaks for research investment and the exclusive right to market orphan-designated drugs for 7 years from the date of marketing approval.[1, 4, 5] Such market exclusivity would allow manufacturers to charge high prices for their rare disease drug product even in the absence of patent protection and despite limited health gain.[5, 6, 7, 8, 9]

Pharmaceutical companies can apply for orphan designation from the Food and Drug Administration (FDA) based on either showing that the targeted condition affects fewer than 200,000 patients annually in the US, or showing no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the US, along with providing a medically plausible basis for believing that the drug would aid in the condition's treatment, prevention, or diagnosis.[10, 11]

In the European Union (EU), the European Medicines Agency (EMA) also designates drugs that target rare diseases with special status.[12] To qualify, a drug must be intended for the treatment of a disease that is life-threatening or chronically debilitating with an EU prevalence of less than 5 in 10,000, or it must be unlikely that marketing of the drug would generate sufficient returns to justify the investment needed for its development.[13, 14, 15] In addition, no satisfactory method of treatment of the condition concerned is already on the market, or, if such a method exists, the new drug must be of significant benefit to those affected by the condition.[11] Like in the US, sponsors of designated orphan drugs in the EU earn certain incentives, including administrative regulatory fee reductions and market exclusivity.[11, 16, 15] Thus, while most prerequisites for orphan disease drug designation between the US and the EU are comparable, the major difference is that the EU requires demonstration of significant benefit in case the drug targets the same indication as a drug already on the market.

Expenditure on cancer drugs dominate pharmaceutical expenditure in developed markets, with world-wide sales at $107 billion in 2015, an increase of 11.4% since 2014.[8, 17, 18] In addition, global spending on orphan-designated drugs will reach $178 billion per year by 2020, much of which will also be drugs for cancer patients.[8]

To determine whether differences in the design of the Orphan Drug Act in the US and EU lead to variations in the application of the statutory incentives, we reviewed all cancer drugs for which indications have been approved with this special status between 2008 – 2017 by the FDA and then determined whether these cancer drugs had also been approved with the same status by the EMA.

Methods

We first searched and identified on the FDA's publicly accessible Orphan Drug Product Designation Database all cancer drugs with orphan status approved by the FDA between 1 January 2008 and 31 December 2017.[19] The approval could have been for an initial or supplementary indication. Cancer drugs with approval for different indications were counted separately for each cancer indication. For example, bevacizumab (Avastin) was approved with orphan status for, among other things, treatment of patients with ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and glioblastoma. Cancer drugs with orphan status that were approved by the FDA for benign tumors as well as combined therapies (e.g., dabrafenib and trametinib [Mekinist]) were not included in our analysis. From two FDA data sources—the Orphan Drug Product Designation Database and Drugs@FDA—we extracted the active ingredient, trade name, orphan designation, approval date, and approved indication.[19, 20]

We then searched on the database of the EMA, the European public assessment reports (EPAR), to determine whether the FDA-approved cancer drugs with orphan status in our cohort were also approved by the EMA (with or without orphan status) as of 1 August 2018. We assumed, as in the study of Giannuzzi et al., that the same drug is available both in the EU and US if the active substance, the therapeutic indication and the Marketing Authorization Holder are the same between both territories.[21] If so, we extracted the same data as from the FDA sources.

Descriptive statistics were performed for the recorded variables. Trends across time and indications of cancer drugs with orphan designation were analyzed descriptively and in comparison between the EU and US.

Patient and Public Involvement

No patients or members of the public were involved in the design and conception of this study.

Results

The FDA approved 135 cancer drug indications with orphan drug designations that met our inclusion criteria. Among this sample, 101 (75%) were also approved by the EMA by 1 August 2018, including drugs with and without such a designation by the EMA (see **Appendix**). Two indications were refused market approval in the EU: romidepsin (Istodax) was refused for treatment of non-Hodgkin's lymphoma, and pralatrexate (Folotyn) for treatment of T-cell lymphoma. Sponsors withdrew their market application for 4 indications, including dinutuximab (Unituxin) for treatment of neuroblastoma was withdrawn due to the inability to supply the drug in sufficient quantities for meeting the demands and omacetaxine (Synribo) for treatment of myelogenous leukemia because of inability to address the issues identified by the EMA within the timeframe allowed.[22]

Among the 101 cancer indications that were designated with orphan drug status by the FDA and also approved by the EMA, 46 were approved for first-line therapy while 55 were indicated for second-, third-, or fourth-line therapy. Forty-five were approved for supplementary (extended) indications of already-approved drugs. There was a substantial increase in designations over time. In the US, 2 approved cancer drug indications were designated with orphan status in 2008, while 16 were approved in 2016 (**Figure 1**).

Eighty of the 101 approved cancer drug indications were first approved in the US, while market approval first took place by the EMA for the other 21. In 81% (65/80), approval in one jurisdiction followed less than a year after market authorization in the other jurisdiction. For example, nivolumab (Opdivo) was approved in the US in December 2017. Approval by the EMA followed less than one year later in June 2018 (see **Appendix**).

Among the 101 orphan drug designated approved cancer conditions, 40% (40/101) were approved for biomarker-derived indications. A biomarker-derived indication is any drug indication approved based on its efficacy in a subset of a more prevalent disease characterized by a particular genetic variant.[23] Examples for approved biomarker-derived indications in our study are nivolumab (Opdivo) for the treatment of BRAF V600 mutated melanoma, or ceritinib (Zykadia) for the treatment of ALK+ non-small cell lung cancer (NSCLC), afatinib (Gilotrif) for EGFR mutated NSCLC and osimertinib (Tagrisso) for EGFR mutated NSCLC. The number of approved biomarker-defined indications with orphan drug designation has increased over the past years in the US (**Figure 2**). Only one biomarker-derived cancer indication was approved with orphan drug designation in 2008, while 8 were approved with orphan status in 2017. By contrast, only 10% (10/101) of approved cancer drug indications by the EMA were orphan designated biomarker-defined subsets of disease. For example, afatinib (Gilotrif) and osimertinib (Tagrisso) got approval in both the US and the EU, however, they only got orphan designation in the US.

Only 41 of the 101 cancer indications with orphan designation by the FDA were also designated with orphan status at the time of market approval by the EMA. While most of the 60 remaining products never received an orphan drug designation in the EU, 4 drugs had their designations withdrawn by the EMA or the sponsor, including olaparib (Lynparza) for treatment of primary peritoneal cancer and later treatment of ovarian cancer and fallopian tube cancer, as well as bosutinib (Bosulif) for treatment of chronic myelogenous leukemia.

The approved cancer drug indications can be differentiated into solid and non-solid tumors.[9, 24, 25, 26] The majority (47/60, 78%) of approved cancer drugs that were only approved in the US with orphan status were indicated for solid tumors, while 22% (13/60) of approved cancer drugs had indications for non-solid tumors. Most frequently approved indications with orphan drug designation for solid tumors were melanoma (13 indications) followed by non-small cell lung cancer (11 indications), gastrointestinal cancer (5 indications), ovarian cancer (3 indications), fallopian tube cancer (3 indications), and peritoneal cancer (3 indications). Most approved cancer indications with orphan designation for non-solid tumors by the FDA were chronic myelogenous lymphoma (3 indications), multiple myeloma (2 indications), Hodgkin lymphoma (2 indications), chronic lymphocytic lymphoma (2 indications), and acute lymphocytic lymphoma (2 indications) (**Figure 3**).

By contrast, out of those approved cancer drugs that were designated with orphan status by both the FDA and the EMA, 20% (8/41) were indicated for solid tumors, and 80% (33/41) for non-solid tumors. Thyroid cancer (3 indications), ovarian cancer (2 indications), and soft tissue sarcoma (2 indications) were the most frequent solid tumors approved in both jurisdictions with orphan drug status. For non-solid tumors, multiple myeloma (8 indications), chronic lymphocytic lymphoma (8 indications) and acute lymphocytic lymphoma (4 indications) were the most frequently approved cancer drug indications with orphan designation (**Figure 4**).

Discussion

This review of cancer drugs newly approved with Orphan Drug Act designations by the FDA from 2008 through 2017 reveals important differences with respect to their approvals by the EMA. Less than 50% of cancer drugs with orphan designation by the FDA received such status in the EMA. Our results are consistent with other studies showing that the US has more orphan drug designations in general and specifically for oncology drugs compared to the EU.[21, 27, 28] Drugs that targeted biomarker-defined subsets of common cancer types often received orphan status in the US, but did not get similar status in the EU.

The number of drugs targeting subpopulations of specific cancers has increased over the last decade with a simultaneous increase in the number of orphan designation by the FDA for drugs indicated for cancers defined as biomarker-based subsets of more common cancers.[23, 29, 30, 31] However, it is interesting to note that the EMA does not follow this pattern (**Figure 2**). Among the 101 orphan-designated drugs from 2008 through 2017, 40% (40/101) were approved for indications defined in part by biomarkers by the FDA, as compared to only 10% (10/101) by the EMA. For example, the FDA approved alectinib (Alecensa) and ceritinib (Zykadia) to treat ALK+ non-small cell lung cancer, crizotinib (Xalkori) to treat ROS1-positive non-small cell lung cancer, and dabrafenib (Tafinlar) to treat BRAF V600E mutated metastatic melanoma.[23, 32] However, none of these drugs were designated with orphan status by the EMA (see **Figure 4** and **Appendix**).

Drugs receiving designations in both settings were more likely to focus on truly rare cancers, such as multiple myeloma or follicular lymphoma. In the EU, the use of biomarkers to identify a subset of patients for whom the drug can be used appears to generally not be accepted as a basis for receiving orphan designation.[33, 34] However, biomarker-derived cancer drugs can still get orphan status in the EU if, among other things, it is unlikely that marketing of the drug would generate sufficient

returns to justify the investment needed for its development and the sponsor provides scientific evidence that the activity of the product would not be shown in the larger population.[35]

One important reason for the different application of "orphan status" in the US and the EU could be the different legal prerequisites for orphan designation. The demonstration of "significant benefit" is mandatory for drugs to be designated with orphan status by the EMA compared to those drugs already on the market targeting the same disease.[15, 36] "Significant benefit" means that a drug has a clinically relevant advantage or makes a major contribution to patients' care, compared with existing drugs already on the market that target the same condition.[33, 37] Significant benefit is a higher standard than the positive benefit-risk assessment that must be demonstrated by the sponsor in the marketing approval process, which does not involve an obligation to show that such a drug is more beneficial than all other methods for treating the same condition.[19] Significant benefit is required at the time of orphan designation, when it can be supported by preclinical studies, and at the time of marketing approval, when clinical data are needed.[36] Our study has shown that a few drugs had their orphan drug designations withdrawn during the marketing approval process, including olaparib (Lynparza) for treatment of primary peritoneal cancer, ovarian cancer, and fallopian tube cancer, and bosutinib (Bosulif) for treatment of chronic myelogenous leukemia. Adding a prerequisite of "significant benefit" to maintain orphan drug designation at the time of FDA approval in the US could help prevent non-first-in-class drugs targeting rare diseases from earning the same incentives as a presumptively more clinically important first-in-class drug for a rare disease. If the second-to-market product offered significant benefits over available treatments, it would get to keep its designation.

Strengths and weaknesses of this study

Our study reveals important new differences of approved cancer drugs with orphan designation between the US and the EU allowing policy implications for the US in order to ensure that only truly rare diseases will be designated orphan status for which research investment is limited.

This study has certain limitations. It was restricted to cancer drugs, and so is not generalizable to other drug classes. Also, we did not investigate whether all approved cancer drugs with orphan designation by the EMA between those same years also received orphan status by the FDA. Therefore, it may be possible that certain cancer drugs with orphan designation by the EMA did not get orphan designation by the FDA.

Conclusion

The Orphan Drug Act in the US was intended to encourage drug development for rare conditions with unmet medical needs. We found that the FDA approves more drugs with such designations for cancer subgroups compared to the EMA. The statute could be revised to ensure it applies to truly rare diseases for which research investment is limited. Other changes to the US Orphan Drug Act could include assessing whether there is "significant benefit" at the time of approval if treatments already exist for a disease targeted by a new drug. Implementation of these reforms could help to improve the development of innovative cancer drugs and by encouraging more resources to be directed to rare cancers that lack effective treatments.

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Figure 1. Approved cancer drug indications with orphan drug designation by the FDA from 2008 through 2017 that were also approved by the EMA (N=101).
X-axis: year of marketing approval by the FDA; y-axis: number of approved cancer indications with orphan drug designation by the FDA.

Figure 2. Numbers of FDA- and EMA-approved drugs indicated for biomarker-defined orphan cancer indications from 2008 through 2017.
X-axis: year of marketing approval by the FDA and EMA; y-axis: number of approved biomarker-derived cancer indications with orphan drug designation; blue = Approved biomarker-derived cancer indications with orphan designation by the FDA; orange = Approved biomarker-derived cancer indications with orphan designation by the EMA.

Figure 3. FDA-approved solid and non-solid tumor cancer drug indications with orphan drug designation.
ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; NSCLC = non-small cell lung cancer.

Figure 4. FDA- and EMA-approved solid and non-solid tumor cancer drug indications with orphan drug designation.
ALCL = anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; AML = acute myeloid lymphoma; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; SLL = small lymphocytic lymphoma; cut. T-cell lymphoma = Cutaneous T-cell lymphoma.

Figure 1. Approved cancer drug indications with Orphan Drug Act designation by the FDA from 2008 through 2017 that were also approved by the EMA (N=101).

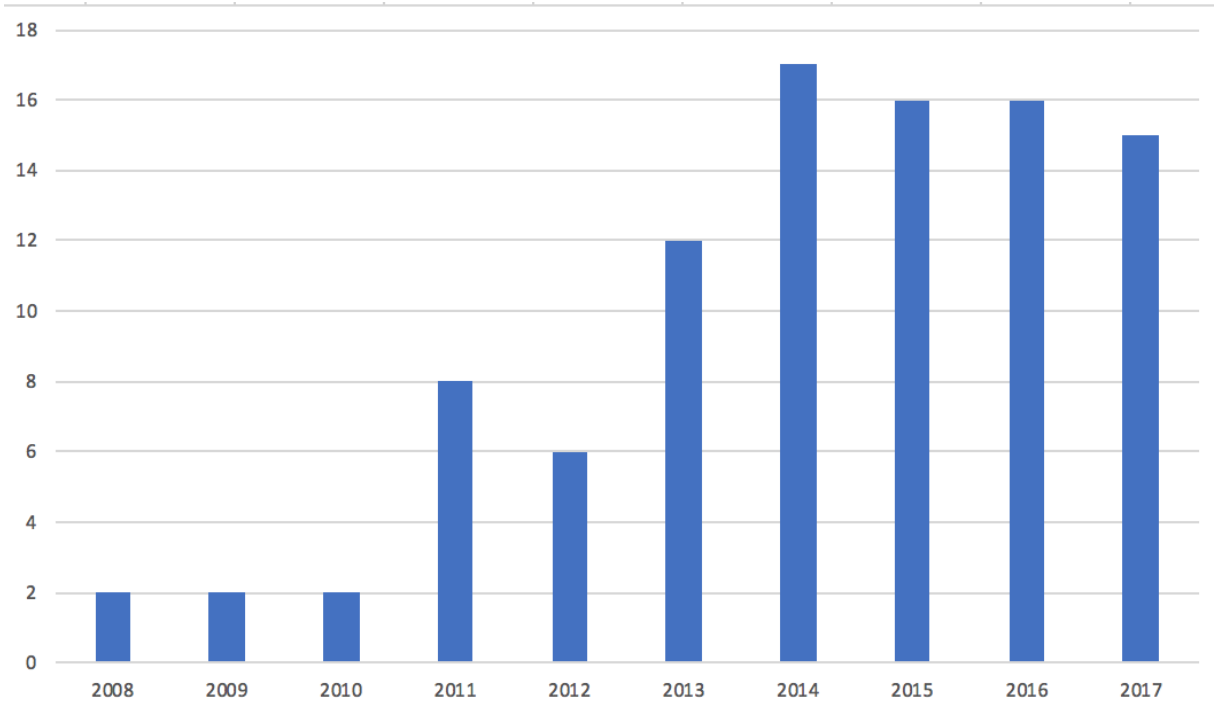

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Figure 2. Numbers of FDA- and EMA-approved drugs indicated for biomarker-defined orphan cancer indications from 2008 through 2017.

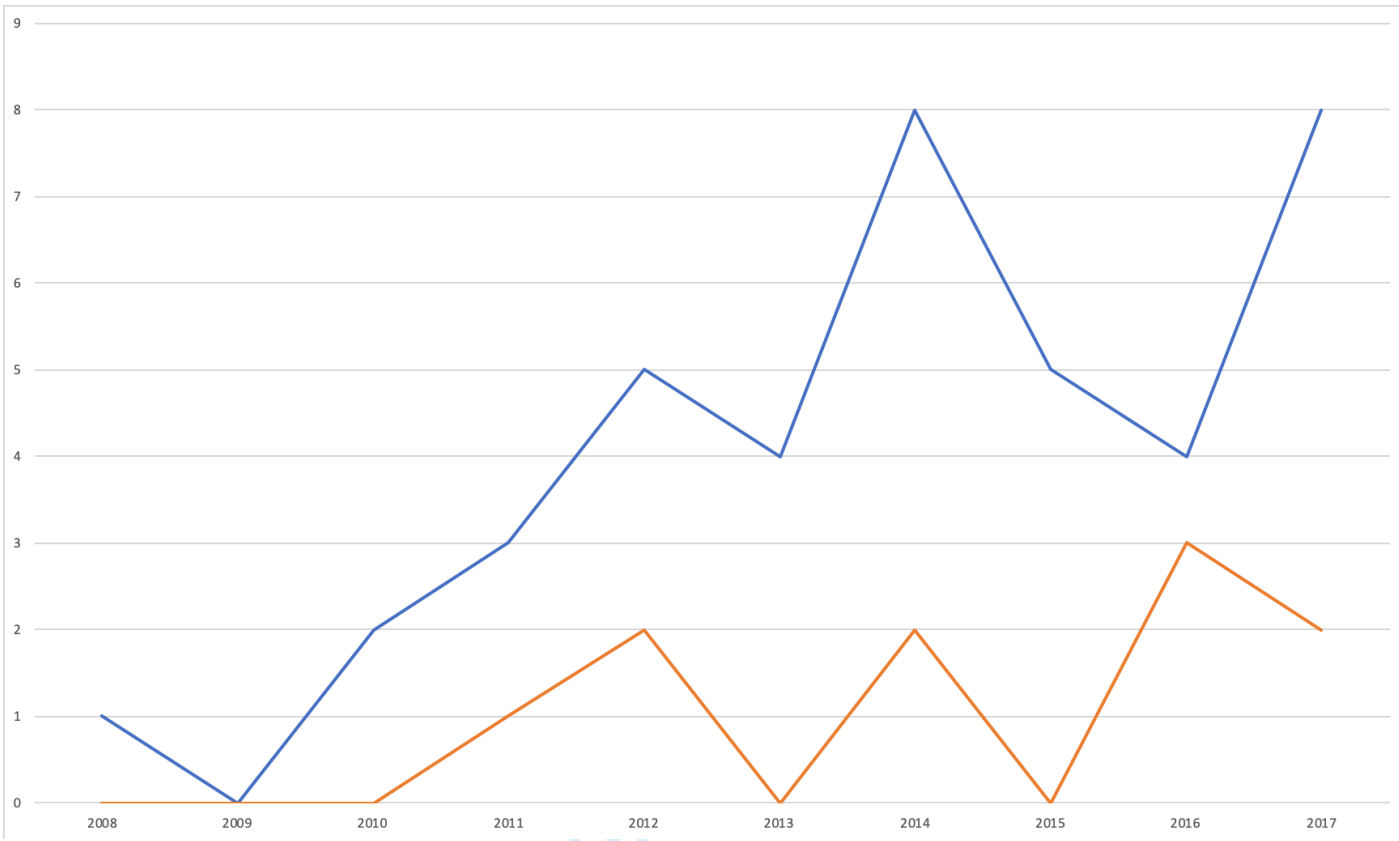

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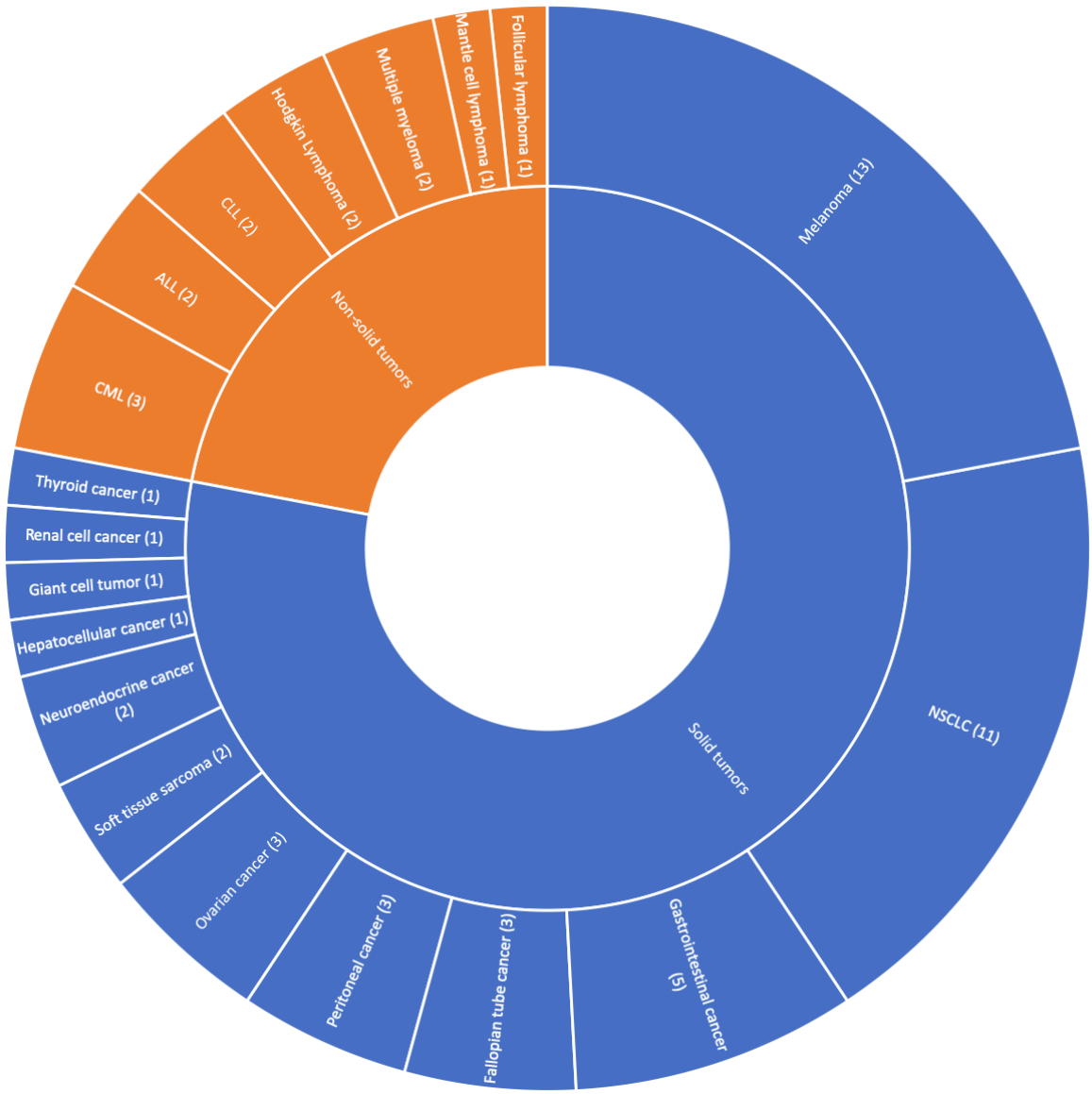
Figure 3. FDA-approved solid and non-solid tumor cancer drug indications with Orphan Drug Act designation.



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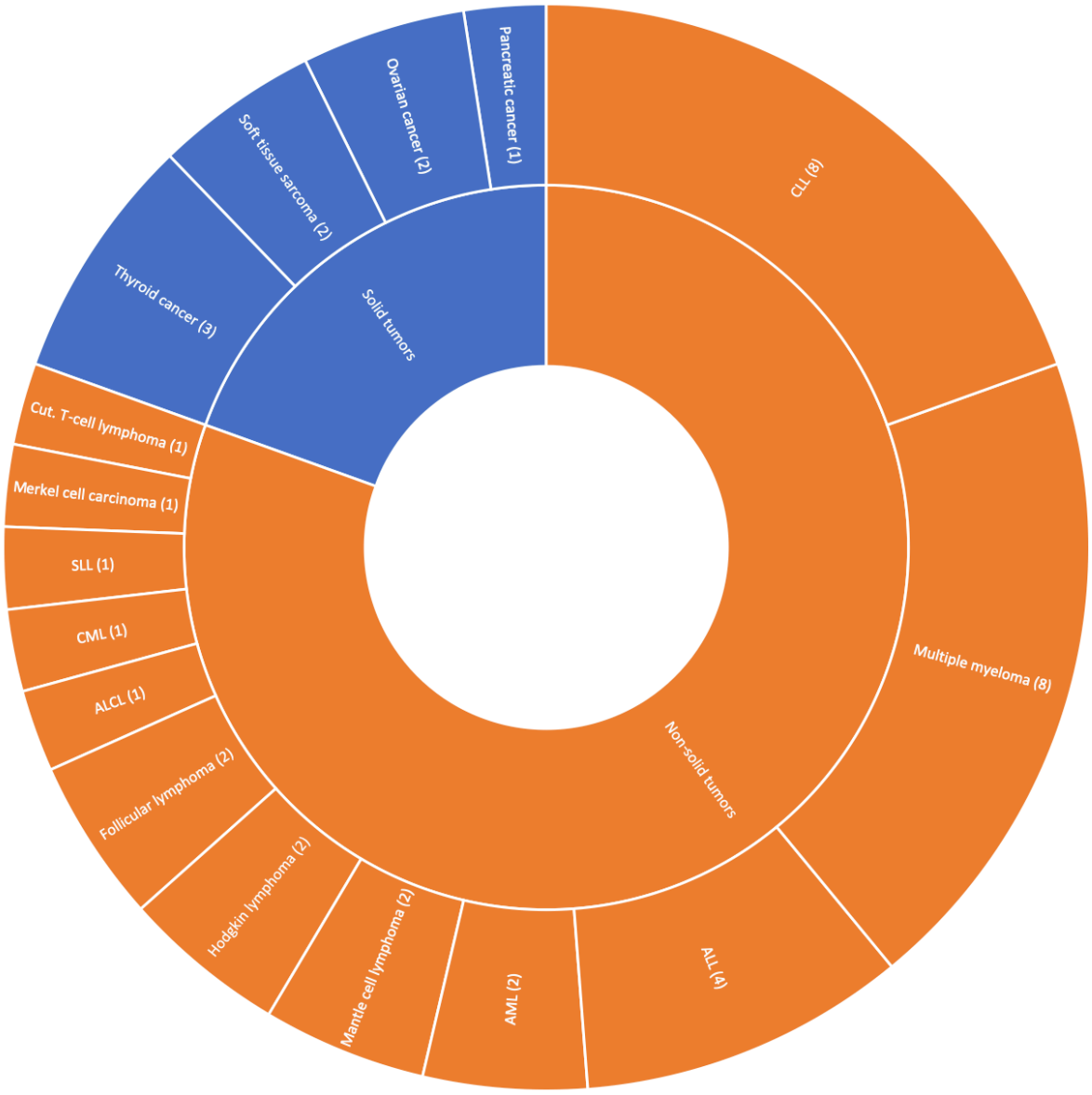

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	Cancer Drug Indications with Orphan Designation by the FDA (2008 - 2017) and Comparison with the EMA					
	FDA				**EMA**	
	Generic Name	**Trade Name**	**Marketing Approval Date**	**Designation**	**Orphan drug Status**	**Approval Date**
1	**nivolumab**	Opdivo	12/20/2017	Treatment of Stage IIb to IV melanoma	no	06/28/2018
2	**bosutinib**	Bosulif	12/19/2017	Treatment of chronic myelogenous leukemia	no	04/23/2018
3	**obinutuzumab**	Gazyva	11/16/2017	Treatment of follicular lymphoma	yes	09/18/2017
4	**Brentuximab vedotin**	Adcetris	11/09/2017	Treatment of primary cutaneous CD30-positive T-cell lymphoproliferative disorders	yes	12/15/2017
5	**dasatinib**	Sprycel	11/09/2017	Treatment of chronic myelogenous leukemia	no	07/02/2018
6	**alectinib**	Alecensa	11/06/2017	Treatment of ALK-positive non-small cell lung cancer	no	12/18/2017
7	**acalabrutinib**	Calquence	10/31/2017	Treatment of mantle cell lymphoma	no approval	
8	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of follicular lymphoma	no approval	
9	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of diffuse large B-cell lymphoma	no approval	
10	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of primary mediastinal B-cell lymphoma	no approval	
11	**pembrolizumab**	Keytruda	09/22/2017	Treatment of gastric cancer, including gastroesophageal junction adenocarcinoma	no approval	
12	**nivolumab**	Opdivo	09/22/2017	Treatment of hepatocellular carcinoma	no approval	
13	**copanlisib**	Aliqopa	09/14/2017	Treatment of follicular lymphoma	no approval	
14	**Gemtuzumab ozogamicin**	Mylotarg	09/01/2017	Treatment of acute myeloid leukemia	yes	04/19/2018
15	**Tisagenlecleucel**	Kymriah	08/30/2017	For the treatment of Acute Lymphoblastic Leukemia	no approval	

16	**inotuzumab ozogamicin**	Besponsa	08/17/2017	Treatment of B-cell acute lymphoblastic leukemia	yes	06/29/2017
17	**olaparib**	Lynparza	08/17/2017	Treatment of primary peritoneal cancer	no	12/16/2014
18	**olaparib**	Lynparza	08/17/2017	Treatment of ovarian cancer	no	12/16/2014
19	**olaparib**	Lynparza	08/17/2017	Treatment of Fallopian Tube Cancer	no	12/16/2014
20	**Cytarabine:daunorubicin liposome injection**	Vyxeos	08/03/2017	Treatment of acute myeloid leukemia	no approval	
21	**enasidenib**	Idhifa	08/01/2017	Treatment of acute myelogenous leukemia	no approval	
22	**ipilimumab**	Yervoy	07/21/2017	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no	05/31/2018
23	**daratumumab**	Darzalex	06/16/2017	Treatment of multiple myeloma	no approval	
24	**ceritinib**	Zykadia	05/26/2017	Treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase(ALK)-positive	no	06/23/2017
25	**brigatinib**	Alunbrig	04/28/2017	Treatment of anaplastic lymphoma kinase-positive (ALK+), c-ros 1 oncogene positive (ROS1+), or epidermal growth factor receptor positive (EGFR+) non-small cell lung cancer (NSCLC).	no approval	
26	**midostaurin**	Rydapt	04/28/2017	Treatment of acute myeloid leukemia	yes	09/18/2017
27	**regorafenib**	Stivarga	04/27/2017	Treatment of hepatocellular carcinoma	no	08/02/2017
28	**nivolumab**	Opdivo	04/25/2017	Treatment of Hodgkin lymphoma	no approval	
29	**methotrexate oral solution**	Xatmep	04/25/2017	Treatment of acute lymphoblastic leukemia in pediatric patients (0 through 16 years of age)	no	03/29/2017
30	**niraparib**	Zejula	03/27/2017	Treatment of ovarian cancer	yes	11/16/2017
31	**avelumab**	Bavencio	03/23/2017	Treatment of merkel cell carcinoma.	yes	09/18/2017
32	**pembrolizumab**	Keytruda	03/14/2017	Treatment of Hodgkin lymphoma	no	05/02/2017

33	**lenalidomide**	Revlimid	02/22/2017	Treatment of multiple myeloma	yes	02/23/2017
34	**ibrutinib**	Imbruvica	01/18/2017	Treatment of patients with extranodal marginal zone lymphoma (mucosa associated lymphoid tissue [MALT type] lymphoma)	no approval	
35	**ibrutinib**	Imbruvica	01/18/2017	Treatment of splenic marginal zone lymphoma	no approval	
36	**ibrutinib**	Imbruvica	01/18/2017	Treatment of nodal marginal zone lymphoma	no approval	
37	**rucaparib**	Rubraca	12/19/2016	Treatment of ovarian cancer	yes	05/24/2018
38	**bevacizumab**	Avastin	12/06/2016	Therapeutic treatment of patients with ovarian cancer	no	02/06/2017
39	**bevacizumab**	Avastin	12/06/2016	Treatment of fallopian tube carcinoma	no	02/06/2017
40	**bevacizumab**	Avastin	12/06/2016	Treatment of primary peritoneal carcinoma.	no	02/06/2017
41	**daratumumab**	Darzalex	11/21/2016	Treatment of multiple myeloma	yes	04/28/2017
42	**olaratumab**	Lartruvo	10/19/2016	Treatment of soft tissue sarcoma	yes	11/09/2016
43	**nivolumab**	Opdivo	05/17/2016	Treatment of Hodgkin lymphoma	no	06/19/2015
44	**ibrutinib**	Imbruvica	05/06/2016	Treatment of small lymphocytic lymphoma	yes	06/26/2016
45	**afatinib**	Gilotrif	04/15/2016	Treatment of non-small cell lung cancer with squamous histology.	no	03/31/2016
46	**venetoclax**	Venclexta	04/11/2016	Treatment of chronic lymphocytic leukemia	yes	12/05/2016
47	**crizotinib**	Xalkori	03/11/2016	Treatment of ALK-positive, MET-positive, or ROS-positive non-small cell lung cancer	no	08/25/2016
48	**ibrutinib**	Imbruvica	03/04/2016	Treatment of chronic lymphocytic leukemia (CLL)	yes	05/26/2016
49	**everolimus**	Afinitor	02/26/2016	Treatment of neuroendocrine tumors of gastroinstestinal or lung origin	no	05/26/2016
50	**obinutuzumab**	Gazyva	02/26/2016	Treatment of follicular lymphoma	yes	06/13/2016

51	**eribulin mesylate**	Halaven	01/28/2016	Treatment of soft tissue sarcoma	no	05/02/2016
52	**ofatumumab**	Arzerra	01/19/2016	Treatment of chronic lymphocytic leukemia	yes	12/08/2016
53	**pembrolizumab**	Keytruda	12/18/2015	Treatment of Stage IIB through IV malignant melanoma	no	07/17/2015
54	**alectinib**	Alecensa	12/11/2015	Treatment of ALK-positive non-small cell lung cancer	no	02/16/2017
55	**bendamustine for 50ml admixture**	Bendeka	12/07/2015	Treatment of Follicular Lymphoma, Small Lymphocytic Lymphoma, Lymphoplasmacytic Lymphoma, Splenic Marginal Zone Lymphoma, Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoma Tissue (MALT), and Nodal Marginal Zone Lymphoma (Collectively Indolent B-cell Non-Hodgkin's Lymphoma)	no approval	
56	**bendamustine for 50 ml admixture**	Bendeka	12/07/2015	Treatment of chronic lymphocytic leukemia	no approval	
57	**elotuzumab**	Empliciti	11/30/2015	Treatment of multiple myeloma	no	05/11/2016
58	**necitumumab**	n/a	11/24/2015	Treatment of squamous non-small cell lung cancer	no	02/15/2016
59	**ixazomib citrate**	Ninlaro	11/20/2015	Treatment of multiple myeloma	yes	11/21/2016
60	**daratumumab**	Darzalex	11/16/2015	Treatment of multiple myeloma	yes	05/20/2016
61	**osimertinib**	Tagrisso	11/13/2015	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	no	02/02/2016
62	**cobimetinib**	Cotellic	11/10/2015	Treatment of stage IIb, IIc, III, and IV melanoma with BRAFV600 mutation	no	11/20/2015
63	**ipilimumab**	Yervoy	10/28/2015	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no approval	
64	**talimogene laherparepvec**	Imlygic	10/27/2015	Treatment of stage IIb-stage IV melanoma	no	12/16/2015
65	**trabectedin**	Yondelis	10/23/2015	Treatment of soft tissue sarcoma	yes	09/17/2007

66	**irinotecan liposome injection**	n/a	10/22/2015	Treatment of pancreatic cancer	yes	10/14/2016
67	**brentuximab vedotin**	Adcetris	08/17/2015	Treatment of Hodgkin's lymphoma	yes	06/24/2016
68	**gefitinib**	Iressa	07/13/2015	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	no	06/24/2009
69	**dinutuximab**	Unituxin	03/10/2015	Treatment of neuroblastoma	withdrawal	08/14/2015
70	**panobinostat**	Farydak	02/23/2015	Treatment of multiple myeloma	yes	08/28/2015
71	**lenalidomide**	Revlimid	02/17/2015	Treatment of multiple myeloma	yes	02/19/2015
72	**lenvatinib**	Lenvima	02/13/2015	Treatment of follicullar, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer	yes	05/28/2015
73	**nivolumab**	Opdivo	12/22/2014	Treatment of Stage IIb to IV melanoma	no approval	
74	**olaparib**	Lynparza	12/19/2014	Treatment of ovarian cancer	no	12/16/2014
75	**lanreotide acetate**	Somatuline Depot	12/16/2014	Treatment of neuroendocrine tumors	no approval	
76	**blinatumomab**	Blincyto	12/03/2014	Treatment of acute lymphocytic leukemia	yes	11/23/2015
77	**bevacizumab**	Avastin	11/14/2014	Treatment of fallopian tube carcinoma	no	07/31/2014
78	**bevacizumab**	Avastin	11/14/2014	Treatment of primary peritoneal carcinoma.	no	07/31/2014
79	**bevacizumab**	Avastin	11/14/2014	Therapeutic treatment of patients with ovarian cancer	no	07/31/2014
80	**ramucirumab**	Cyramza	11/05/2014	Treatment of gastric cancer	no	12/19/2014
81	**bortezomib**	Velcade	10/08/2014	Treatment of mantle cell lymphoma.	no	01/30/2015
82	**pembrolizumab**	Keytruda	09/04/2014	Treatment of Stage IIB through IV malignant melanoma	no	07/17/2015
83	**ibrutinib**	Imbruvica	07/28/2014	Treatment of chronic lymphocytic leukemia (CLL)	yes	05/26/2016

84	**idelalisib**	Zydelig	07/23/2014	Treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma	no	09/18/2014
85	**idelalisib**	Zydelig	07/23/2014	Treatment of follicular lymphoma	no	09/18/2014
86	**Belinostat**	Beleodaq	07/03/2014	Treatment of peripheral T-cell lymphoma (PTCL)	not yet approved	
87	**ceritinib**	Zykadia	04/29/2014	Treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase(ALK)-positive	no	05/06/2015
88	**mercaptopurine oral solution**	Purixan	04/28/2014	Treatment of acute lymphoblastic leukemia in pediatric patients	yes	03/09/2012
89	**ramucirumab**	Cyramza	04/21/2014	Treatment of gastric cancer	no	12/19/2014
90	**ofatumumab**	Arzerra	04/17/2014	Treatment of chronic lymphocytic leukemia	yes	06/30/2014
91	**ibrutinib**	Imbruvica	02/12/2014	Treatment of chronic lymphocytic leukemia (CLL)	yes	10/21/2014
92	**trametinib and dabrafenib**	Mekinist And Tafinlar	01/09/2014	Treatment of Stage IIb through IV melanoma.	no	08/25/2015
93	**sorafenib**	Nexavar	11/22/2013	Treatment of medullary thyroid cancer, anaplastic thyroid cancer, and recurrent or metastatic follicular or papillary thyroid cancer	yes	05/23/2014
94	**ibrutinib**	Imbruvica	11/13/2013	Treatment of mantle cell lymphoma	yes	10/21/2014
95	**obinutuzumab**	Gazyva	11/01/2013	Treatment of chronic lymphocytic leukemia	yes	07/23/2014
96	**paclitaxel protein-bound particles**	Abraxane	09/06/2013	Treatment of pancreatic cancer.	no	12/02/2013
97	**afatinib**	Gilotrif	07/12/2013	Treatment of epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC).	no	09/25/2013
98	**denosumab**	Xgeva	06/13/2013	Treatment of patients with giant cell tumor of bone	no	09/01/2014
99	**lenalidomide**	Revlimid	06/05/2013	Treatment of mantle cell lymphoma	yes	07/08/2016
100	**trametinib**	Mekinist	05/29/2013	Treatment of Stage IIb through Stage IV melanoma	no	06/30/2014

101	**dabrafenib**	Tafinlar	05/29/2013	Treatment BRAF V600 mutation positive Stage IIB through IV melanoma	no	08/26/2013
102	**regorafenib**	Stivarga	02/25/2013	Treatment gastrointestinal stromal tumors	no	07/28/2014
103	**pomalidomide**	Pomalyst	02/08/2013	Treatment of multiple myeloma	yes	08/05/2013
104	**imatinib**	Gleevec	01/25/2013	Treatment of Philadelphia-positive acute lymphoblastic leukemia	no	06/27/2013
105	**ponatinib**	Iclusig	12/14/2012	Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL)	yes	7/01/2013
106	**ponatinib**	Iclusig	12/14/2012	Treatment of chronic myeloid leukemia	yes	07/01/2013
107	**cabozantinib**	Cometriq	11/29/2012	Treatment of follicular, medullary and anaplastic thyroid carcinoma and metastatic or locally advanced papillary thyroid cancer.	yes	03/21/2014
108	**omacetaxine mepesuccinate**	Synribo	10/26/2012	Treatment of chronic myelogenous leukemia	withdrawal	
109	**bosutinib**	Bosulif	09/04/2012	Treatment of chronic myelogenous leukemia	no	02/22/2018
110	**vinCRIStine sulfate LIPOSOME injection**	Marqibo	08/09/2012	Treatment of acute lymphoblastic leukemia	no approval	
111	**carfilzomib**	Kyprolis	07/20/2012	Treatment of multiple myeloma	yes	11/19/2015
112	**pazopanib**	Votrient	04/26/2012	Treatment of soft tissue sarcomas	no	08/03/2012
113	**Erwinia L-asparaginase**	Erwinase	11/18/2011	Treatment of acute lymphocytic leukemia.	no approval	
114	**brentuximab vedotin**	Adcetris	08/19/2011	Treatment of Hodgkin's lymphoma	yes	06/24/2016
115	**brentuximab vedotin**	Adcetris	08/19/2011	Treatment of anaplastic large cell lymphoma	yes	10/25/2012
116	**vemurafenib**	Zelboraf	08/17/2011	Treatment of patients with IIb to Stage IV melanoma positive for the BRAF(v600) mutation	no	02/17/2012
117	**romidepsin**	Istodax	06/16/2011	Treatment of non-Hodgkin T-cell lymphomas	refusal	02/12/2013

118	**everolimus**	Afinitor	05/05/2011	Treatment of neuroendocrine tumors of pancreatic origin	no	08/24/2011
119	**levoleucovorin**	Fusilev	04/29/2011	For use in combination chemotherapy with the approved agent 5-fluorouracil in the palliative treatment of metastatic adenocarcinoma of the colon and rectum	withdrawal	
120	**vandetanib**	Caprelsa(R)	04/06/2011	Treatment of patients with follicular thyroid carcinoma, medullary thyroid carcinoma, anaplastic thyroid carcinoma, and locally advanced and metastatic papillary thyroid carcinoma	no	02/17/2012
121	**peginterferon alfa-2b**	Sylatron	03/29/2011	Treatment of malignant melanoma stages IIb through IV.	no	03/09/2010
122	**ipilimumab**	Yervoy	03/25/2011	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no	07/13/2011
123	**crizotinib**	Xalkori	03/11/2011	Treatment of ALK-positive, MET-positive, or ROS-positive non-small cell lung cancer	no	10/23/2012
124	**trastuzumab**	Herceptin	10/20/2010	Treatment of HER2-overexpressing advanced adenocarcinoma of the stomach, including gastroesophageal junction	no	01/19/2010
125	**rituximab**	Rituxan	02/18/2010	Treatment of chronic lymphocytic leukemia	no	06/15/2017
126	**ofatumumab**	Arzerra	10/26/2009	Treatment of chronic lymphocytic leukemia	yes	04/19/2010
127	**pralatrexate**	Folotyn	09/25/2009	Treatment of T-cell lymphoma	refusal	06/21/2012
128	**bevacizumab**	Avastin	07/31/2009	Treatment of renal cell carcinoma	no	01/12/2005
129	**bevacizumab**	Avastin	05/05/2009	Treatment of malignant glioma	not approved	
130	**imatinib mesylate**	Gleevec	12/19/2008	Treatment of gastrointestinal stromal tumors	no	04/29/2009
131	**Fludarabine phosphate oral tablets**	n/a	12/18/2008	Treatment of B-cell chronic lymphocytic leukemia	approved decentralized system (national level)	

132	**bendamustine hydrochloride**	Treanda	10/31/2008	Treatment of Follicular Lymphoma, Small Lymphocytic Lymphoma, Lymphoplasmacytic Lymphoma, Splenic Marginal Zone Lymphoma, Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoma Tissue (MALT), and Nodal Marginal Zone Lymphoma (Collectively Indolent B-cell Non-Hodgkin's Lymphoma)	approved decentralized system (national level)	
133	**bortezomib**	Velcade	06/20/2008	Treatment of multiple myeloma	no	08/29/2008
134	**Bendamustine hydrochloride**	Treanda	03/20/2008	Treatment of chronic lymphocytic leukemia	approved decentralized system (national level)	
135	**Levoleucovorin**	Fusilev	03/07/2008	For use in conjunction with high-dose methotrexate in the treatment of osteosarcoma.	withdrawal	

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3, 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3, 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*3, 4*
Bias	9	Describe any efforts to address potential sources of bias	3-5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3-5
		(*b*) Describe any methods used to examine subgroups and interactions	3-5
		(*c*) Explain how missing data were addressed	3-5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	135 drugs
		(b) Give reasons for non-participation at each stage	3
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3
		(b) Indicate number of participants with missing data for each variable of interest	3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*3*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	4-6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5-6
Generalisability	21	Discuss the generalisability (external validity) of the study results	5-6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Application of Orphan Drug Designation to Cancer Treatments (2008 – 2017): A Comprehensive and Comparative Analysis of the US and EU

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Study concept and design: Kesselheim, Vokinger
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Transparency declaration: Dr. Vokinger affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Abstract

Objective: To determine differences in the characteristics of cancer drugs designated as orphan drugs by the FDA and EMA.

Design and setting: Identification of all cancer drugs (initial or supplementary indication) with orphan status approved by the FDA between 2008-2017 based on publicly accessible reports. The European public assessment reports (EPAR) was searched to determine whether these FDA-approved drugs were also approved by the EMA.

Main outcome measures: Extraction of active ingredient, trade name, approval date, and approved indication from two FDA data sources (Orphan Drug Product Designation Database, Drugs@FDA) and comparison with the same data from EPAR.

Results: The FDA approved 135 cancer drugs with orphan indications that met our inclusion criteria, of which 101 (75%) were also approved by the EMA. 80/101 (79%) were first approved in the US. Only 41/101 (41%) also received orphan designation by the EMA. 33/101 (33%) were approved for biomarker-based indications in the US, however, only 9 approved cancer drug indications by the EMA were biomarker-derived drugs. 78% (47/60) of approved cancer drugs that were only approved in the US with orphan status were indicated for solid tumors, 22% (13/60) had indications for non-solid tumors. By contrast, out of those approved cancer drugs that received orphan designation by both agencies, 20% (8/41) were indicated for solid, and 80% (33/41) for non-solid tumors.

Conclusions: Orphan designation was intended to encourage drug development for rare conditions. This study shows that the FDA approves more cancer drugs with such designations compared to the EMA, especially for subgroups of more prevalent cancers. One reason for the difference could be that the EU requires demonstration of significant benefit for drugs that target the same indication as a drug already on the market to earn the orphan designation.

Strengths and Limitations of this Study

Strengths:

- Our methodological and comparative approach (empirical analysis, health policy, comparative health law) enables to find possible solutions of how the US could adopt useful policies applied in the EU and thus improve the development of innovative cancer drugs.
- The inclusion of approved cancer drugs designated with orphan status over a time period of 10 years enables to detect informative trends in the specific jurisdiction (US and EU) as well as meaningful comparisons between the jurisdictions.
- To date, no study analyzed the differences in the application of orphan status on cancer drugs by the FDA and EMA.

Limitations:

- Our study is restricted to cancer drugs, and so is not generalizable to other drug classes.
- We did not investigate whether all approved cancer drugs with orphan designation by the EMA between those same years also received this status by the FDA. Therefore, it may be possible that certain cancer drugs with orphan designation by the EMA did not get this designation by the FDA.

Introduction

The US Congress passed the Orphan Drug Act in 1983 to create incentives for the development of drugs for rare diseases that might not otherwise be financially viable due to small potential patient populations.[1, 2, 3] Among other things, the statutory incentives include providing manufacturers with the opportunity to earn special tax breaks for research investment and the exclusive right to market orphan-designated drugs for 7 years from the date of marketing approval.[1, 4, 5] Such market exclusivity would allow manufacturers to charge high prices for their rare disease drug product even in the absence of patent protection and despite limited health gain.[5, 6, 7, 8, 9]

Pharmaceutical companies can apply for orphan designation from the Food and Drug Administration (FDA) based on either showing that the targeted condition affects fewer than 200,000 patients annually in the US, or showing no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the US, along with providing a medically plausible basis for believing that the drug would aid in the condition's treatment, prevention, or diagnosis.[10, 11]

In the European Union (EU), the European Medicines Agency (EMA) also designates drugs that target rare diseases with special status.[12] To qualify, a drug must be intended for the treatment of a disease that is life-threatening or chronically debilitating with an EU prevalence of less than 5 in 10,000, or it must be unlikely that marketing of the drug would generate sufficient returns to justify the investment needed for its development.[13, 14, 15] In addition, no satisfactory method of treatment of the condition concerned is already on the market, or, if such a method exists, the new drug must be of significant benefit to those affected by the condition.[11] Like in the US, sponsors of designated orphan drugs in the EU earn certain incentives, including administrative regulatory fee reductions and market exclusivity.[11, 16, 15] Thus, while most prerequisites for orphan disease drug designation between the US and the EU are comparable, the major difference is that the EU requires demonstration of significant benefit in case the drug targets the same indication as a drug already on the market.

Expenditure on cancer drugs dominate pharmaceutical expenditure in developed markets, with world-wide sales at $107 billion in 2015, an increase of 11.4% since 2014.[8, 17, 18] In addition, global spending on orphan-designated drugs will reach $178 billion per year by 2020, much of which will also be drugs for cancer patients.[8]

To determine whether differences in the design of the Orphan Drug Act in the US and EU lead to variations in the application of the statutory incentives, we reviewed all cancer drugs for which indications have been approved with this special status between 2008 – 2017 by the FDA and then determined whether these cancer drugs had also been approved with the same status by the EMA.

Methods

We first searched and identified on the FDA's publicly accessible Orphan Drug Product Designation Database all cancer drugs with orphan status approved by the FDA between 1 January 2008 and 31 December 2017.[19] The approval could have been for an initial or supplementary indication. Cancer drugs with approval for different indications were counted separately for each cancer indication. For example, bevacizumab (Avastin) was approved with orphan status for, among other things, treatment of patients with ovarian cancer, fallopian tube cancer, primary peritoneal cancer, and glioblastoma. Cancer drugs with orphan status that were approved by the FDA for benign tumors as well as combined therapies (e.g., dabrafenib and trametinib [Mekinist]) were not included in our analysis. From two FDA data sources—the Orphan Drug Product Designation Database and Drugs@FDA—we extracted the active ingredient, trade name, orphan designation, approval date, and approved indication.[19, 20]

We then searched on the database of the EMA, the European public assessment reports (EPAR), to determine whether the FDA-approved cancer drugs with orphan status in our cohort were also approved by the EMA (with or without orphan status) as of 1 August 2018. Following the methodology of another study, we assumed that the same drug is available both in the EU and US if the active substance, the therapeutic indication and the Marketing Authorization Holder are the same between both territories.[21] If so, we extracted the same data as from the FDA sources.

Descriptive statistics were performed for the recorded variables. Trends across time and indications of cancer drugs with orphan designation were analyzed descriptively and in comparison between the EU and US.

Patient and Public Involvement

No patients or members of the public were involved in the design and conception of this study.

Results

The FDA approved 135 cancer drug indications with orphan drug designations that met our inclusion criteria. Among this sample, 101 (75%) were also approved by the EMA by 1 August 2018, including drugs with and without such a designation by the EMA (see **Appendix**). Two indications were refused market approval in the EU: romidepsin (Istodax) was refused for treatment of non-Hodgkin's lymphoma, and pralatrexate (Folotyn) for treatment of T-cell lymphoma. Sponsors withdrew their market application for 4 indications, including dinutuximab (Unituxin) for treatment of neuroblastoma was withdrawn due to the inability to supply the drug in sufficient quantities for meeting the demands and omacetaxine (Synribo) for treatment of myelogenous leukemia because of inability to address the issues identified by the EMA within the timeframe allowed.[22]

Among the 101 cancer indications that were designated with orphan drug status by the FDA and also approved by the EMA, 46 were approved for first-line therapy while 55 were indicated for second-, third-, or fourth-line therapy. Forty-five were approved for supplementary (extended) indications of already-approved drugs. There was a substantial increase in designations over time. In the US, 2 approved cancer drug indications were designated with orphan status in 2008, while 16 were approved in 2016 (**Figure 1**).

Eighty of the 101 approved cancer drug indications were first approved in the US, while market approval first took place by the EMA for the other 21. In 81% (65/80), approval in one jurisdiction followed less than a year after market authorization in the other jurisdiction. For example, nivolumab (Opdivo) was approved in the US in December 2017. Approval by the EMA followed less than one year later in June 2018 (see **Appendix**).

Among the 101 orphan drug designated approved cancer conditions, 40% (40/101) were approved for biomarker-derived indications. A biomarker-derived indication is any drug indication approved based on its efficacy in a subset of a more prevalent disease characterized by a particular genetic variant.[23] Examples for approved biomarker-derived indications in our study are nivolumab (Opdivo) for the treatment of BRAF V600 mutated melanoma, or ceritinib (Zykadia) for the treatment of ALK+ non-small cell lung cancer (NSCLC), afatinib (Gilotrif) for EGFR mutated NSCLC and osimertinib (Tagrisso) for EGFR mutated NSCLC. The number of approved biomarker-defined indications with orphan drug designation has increased over the past years in the US (**Figure 2**). Only one biomarker-derived cancer indication was approved with orphan drug designation in 2008, while 8 were approved with orphan status in 2017. By contrast, only 10% (10/101) of approved cancer drug indications by the EMA were orphan designated biomarker-defined subsets of disease. For example, afatinib (Gilotrif) and osimertinib (Tagrisso) got approval in both the US and the EU, however, they only got orphan designation in the US.

Only 41 of the 101 cancer indications with orphan designation by the FDA were also designated with orphan status at the time of market approval by the EMA. While most of the 60 remaining products never received an orphan drug designation in the EU, 4 drugs had their designations withdrawn by the EMA or the sponsor, including olaparib (Lynparza) for treatment of primary peritoneal cancer and later treatment of ovarian cancer and fallopian tube cancer, as well as bosutinib (Bosulif) for treatment of chronic myelogenous leukemia.

The approved cancer drug indications can be differentiated into solid and non-solid tumors.[9, 24, 25, 26] The majority (47/60, 78%) of approved cancer drugs that were only approved in the US with orphan status were indicated for solid tumors, while 22% (13/60) of approved cancer drugs had indications for non-solid tumors. Most frequently approved indications with orphan drug designation for solid tumors were melanoma (13 indications) followed by non-small cell lung cancer (11 indications), gastrointestinal cancer (5 indications), ovarian cancer (3 indications), fallopian tube cancer (3 indications), and peritoneal cancer (3 indications). Most approved cancer indications with orphan designation for non-solid tumors by the FDA were chronic myelogenous lymphoma (3 indications), multiple myeloma (2 indications), Hodgkin lymphoma (2 indications), chronic lymphocytic lymphoma (2 indications), and acute lymphocytic lymphoma (2 indications) (**Figure 3**).

By contrast, out of those approved cancer drugs that were designated with orphan status by both the FDA and the EMA, 20% (8/41) were indicated for solid tumors, and 80% (33/41) for non-solid tumors. Thyroid cancer (3 indications), ovarian cancer (2 indications), and soft tissue sarcoma (2 indications) were the most frequent solid tumors approved in both jurisdictions with orphan drug status. For non-solid tumors, multiple myeloma (8 indications), chronic lymphocytic lymphoma (8 indications) and acute lymphocytic lymphoma (4 indications) were the most frequently approved cancer drug indications with orphan designation (**Figure 4**).

Discussion

This review of cancer drugs newly approved with Orphan Drug Act designations by the FDA from 2008 through 2017 reveals important differences with respect to their approvals by the EMA. Less than 50% of cancer drugs with orphan designation by the FDA received such status in the EMA. Our results are consistent with other studies showing that the US has more orphan drug designations in general and specifically for oncology drugs compared to the EU.[21, 27, 28] Drugs that targeted biomarker-defined subsets of common cancer types often received orphan status in the US, but did not get similar status in the EU.

The number of drugs targeting subpopulations of specific cancers has increased over the last decade with a simultaneous increase in the number of orphan designation by the FDA for drugs indicated for cancers defined as biomarker-based subsets of more common cancers.[23, 29, 30, 31] However, it is interesting to note that the EMA does not follow this pattern (**Figure 2**). Among the 101 orphan-designated drugs from 2008 through 2017, 40% (40/101) were approved for indications defined in part by biomarkers by the FDA, as compared to only 10% (10/101) by the EMA. For example, the FDA approved alectinib (Alecensa) and ceritinib (Zykadia) to treat ALK+ non-small cell lung cancer, crizotinib (Xalkori) to treat ROS1-positive non-small cell lung cancer, and dabrafenib (Tafinlar) to treat BRAF V600E mutated metastatic melanoma.[23, 32] However, none of these drugs were designated with orphan status by the EMA (see **Figure 4** and **Appendix**).

Drugs receiving designations in both settings were more likely to focus on truly rare cancers, such as multiple myeloma or follicular lymphoma. In the EU, the use of biomarkers to identify a subset of patients for whom the drug can be used appears to generally not be accepted as a basis for receiving orphan designation.[33, 34] However, biomarker-derived cancer drugs can still get orphan status in the EU if, among other things, it is unlikely that marketing of the drug would generate sufficient

returns to justify the investment needed for its development and the sponsor provides scientific evidence that the activity of the product would not be shown in the larger population.[35]

One important reason for the different application of "orphan status" in the US and the EU could be the different legal prerequisites for orphan designation. The demonstration of "significant benefit" is mandatory for drugs to be designated with orphan status by the EMA compared to those drugs already on the market targeting the same disease.[15, 34, 36] "Significant benefit" means that a drug has a clinically relevant advantage or makes a major contribution to patients' care, compared with existing drugs already on the market that target the same condition.[33, 37] Significant benefit is a higher standard than the positive benefit-risk assessment that must be demonstrated by the sponsor in the marketing approval process, which does not involve an obligation to show that such a drug is more beneficial than all other methods for treating the same condition.[19] Significant benefit is required at the time of orphan designation, when it can be supported by preclinical studies, and at the time of marketing approval, when clinical data are needed.[36] Our study has shown that a few drugs had their orphan drug designations withdrawn during the marketing approval process, including olaparib (Lynparza) for treatment of primary peritoneal cancer, ovarian cancer, and fallopian tube cancer, and bosutinib (Bosulif) for treatment of chronic myelogenous leukemia in the EU.

Adding a prerequisite of "significant benefit" to maintain orphan drug designation at the time of FDA approval in the US could help prevent non-first-in-class drugs targeting rare diseases from earning the same incentives as a presumptively more clinically important first-in-class drug for a rare disease. If the second-to-market product offered significant benefits over available treatments, it would get to keep its designation.

Strengths and weaknesses of this study

Our study reveals important new differences of approved cancer drugs with orphan designation between the US and the EU allowing policy implications for the US in order to ensure that only truly rare diseases will be designated orphan status for which research investment is limited.

This study has certain limitations. It was restricted to cancer drugs, and so is not generalizable to other drug classes. Also, we did not investigate whether all approved cancer drugs with orphan designation by the EMA between those same years also received orphan status by the FDA. Therefore, it may be possible that certain cancer drugs with orphan designation by the EMA did not get orphan designation by the FDA.

Conclusion

The Orphan Drug Act in the US was intended to encourage drug development for rare conditions with unmet medical needs. We found that the FDA approves more drugs with such designations for cancer subgroups compared to the EMA. The statute could be revised to ensure it applies to truly rare diseases for which research investment is limited. Other changes to the US Orphan Drug Act could include assessing whether there is "significant benefit" at the time of approval if treatments already exist for a disease targeted by a new drug. Implementation of these reforms could help to improve the development of innovative cancer drugs and by encouraging more resources to be directed to rare cancers that lack effective treatments.

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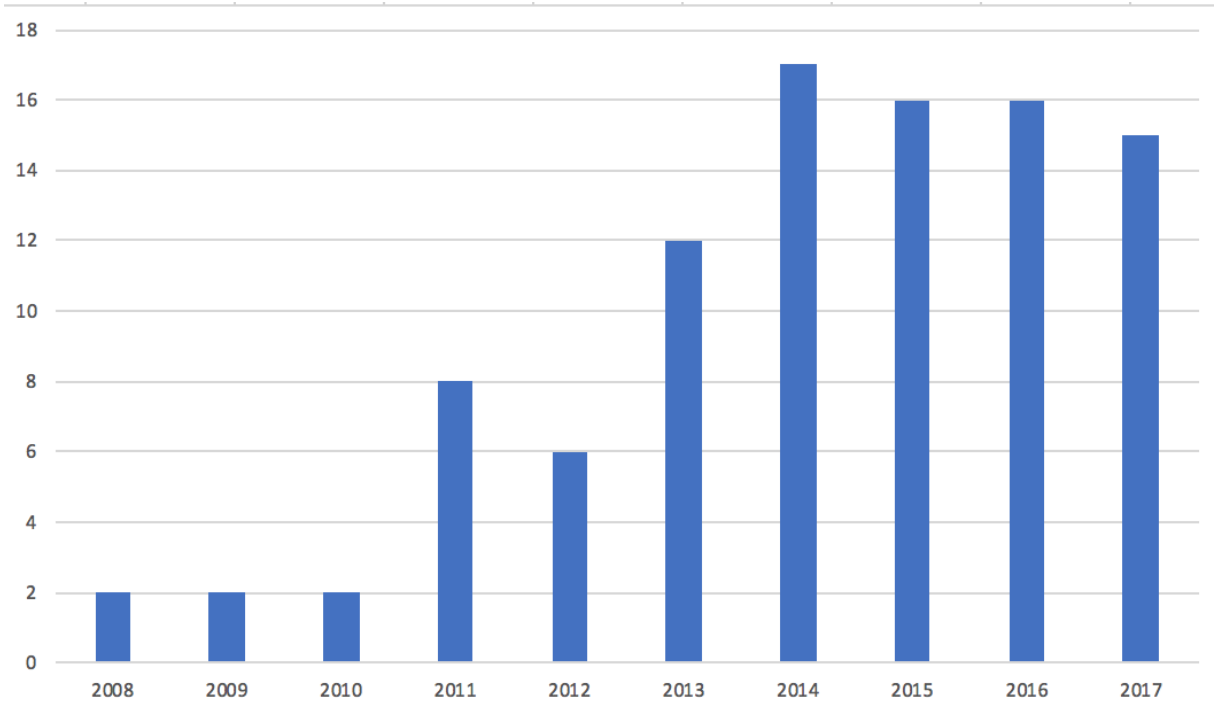
Figure 1. Approved cancer drug indications with orphan drug designation by the FDA from 2008 through 2017 that were also approved by the EMA (N=101).
X-axis: year of marketing approval by the FDA; y-axis: number of approved cancer indications with orphan drug designation by the FDA.

Figure 2. Numbers of FDA- and EMA-approved drugs indicated for biomarker-defined orphan cancer indications from 2008 through 2017.
X-axis: year of marketing approval by the FDA and EMA; y-axis: number of approved biomarker-derived cancer indications with orphan drug designation; blue = Approved biomarker-derived cancer indications with orphan designation by the FDA; orange = Approved biomarker-derived cancer indications with orphan designation by the EMA.

Figure 3. FDA-approved solid and non-solid tumor cancer drug indications with orphan drug designation.
ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; NSCLC = non-small cell lung cancer.

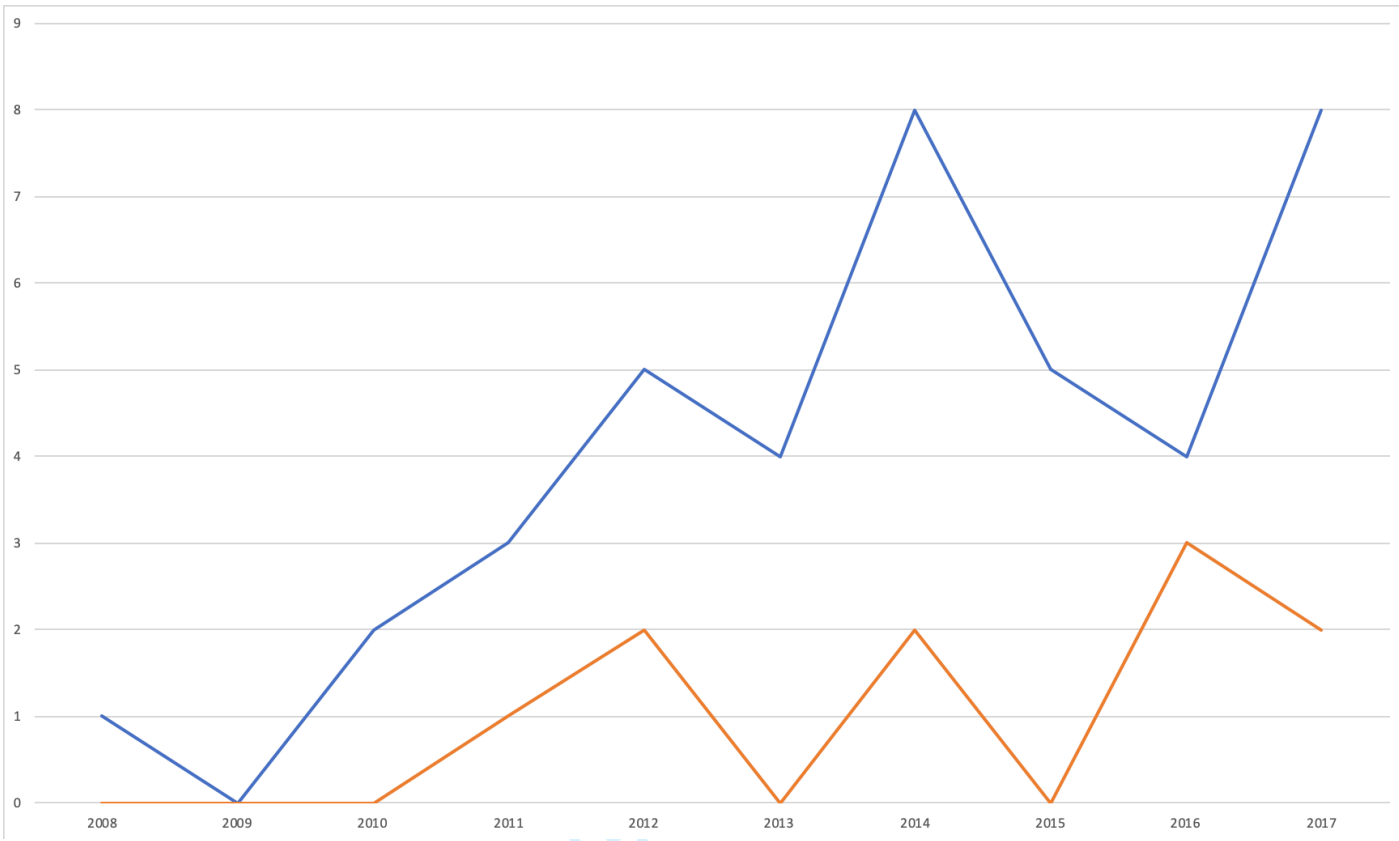
Figure 4. FDA- and EMA-approved solid and non-solid tumor cancer drug indications with orphan drug designation.
ALCL = anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; AML = acute myeloid lymphoma; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; SLL = small lymphocytic lymphoma; cut. T-cell lymphoma = Cutaneous T-cell lymphoma.

Figure 1. Approved cancer drug indications with Orphan Drug Act designation by the FDA from 2008 through 2017 that were also approved by the EMA (N=101).



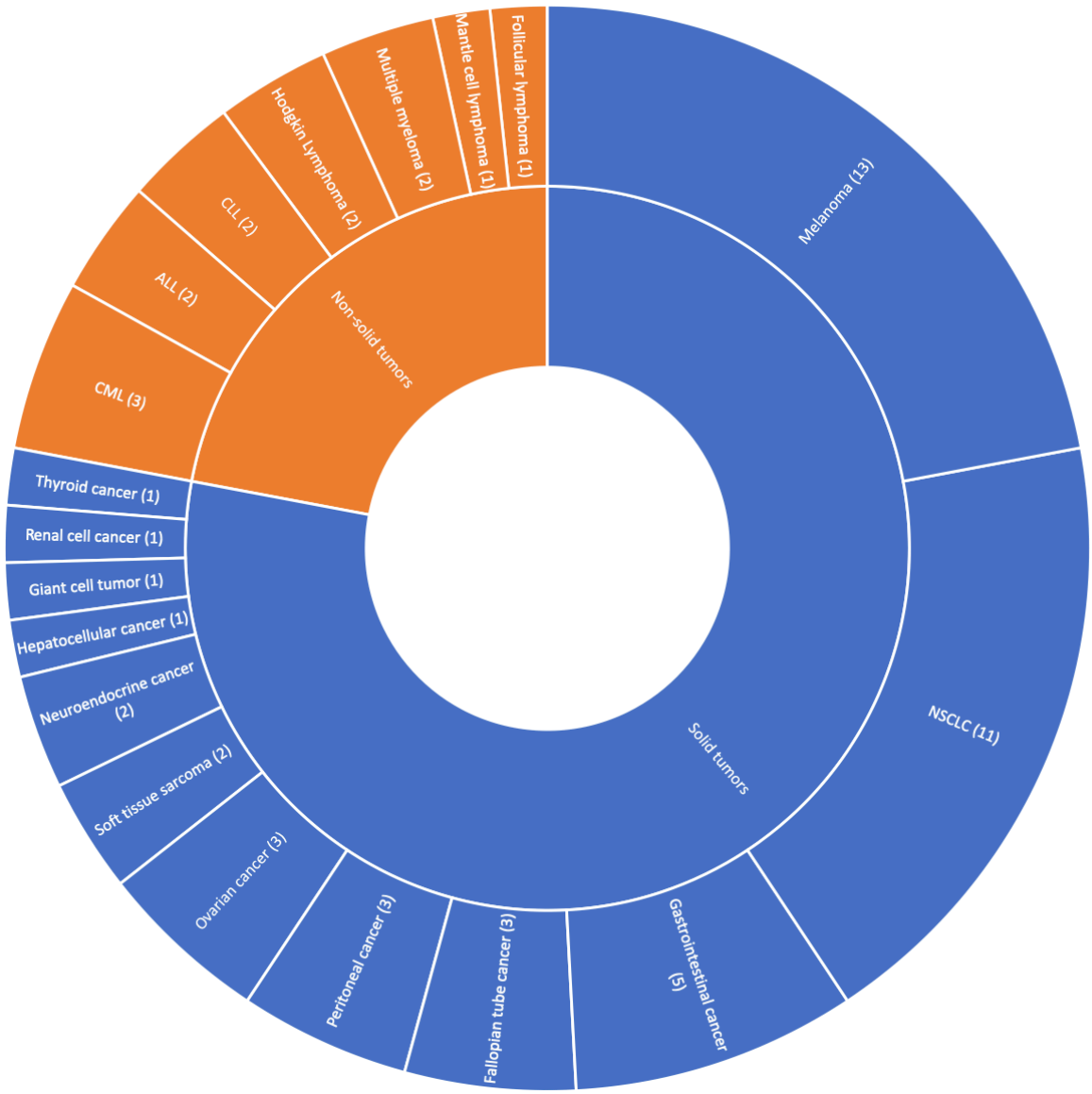
X-axis: year of marketing approval by the FDA; y-axis: number of approved cancer indications with orphan drug designation by the FDA.

Figure 2. Numbers of FDA- and EMA-approved drugs indicated for biomarker-defined orphan cancer indications from 2008 through 2017.



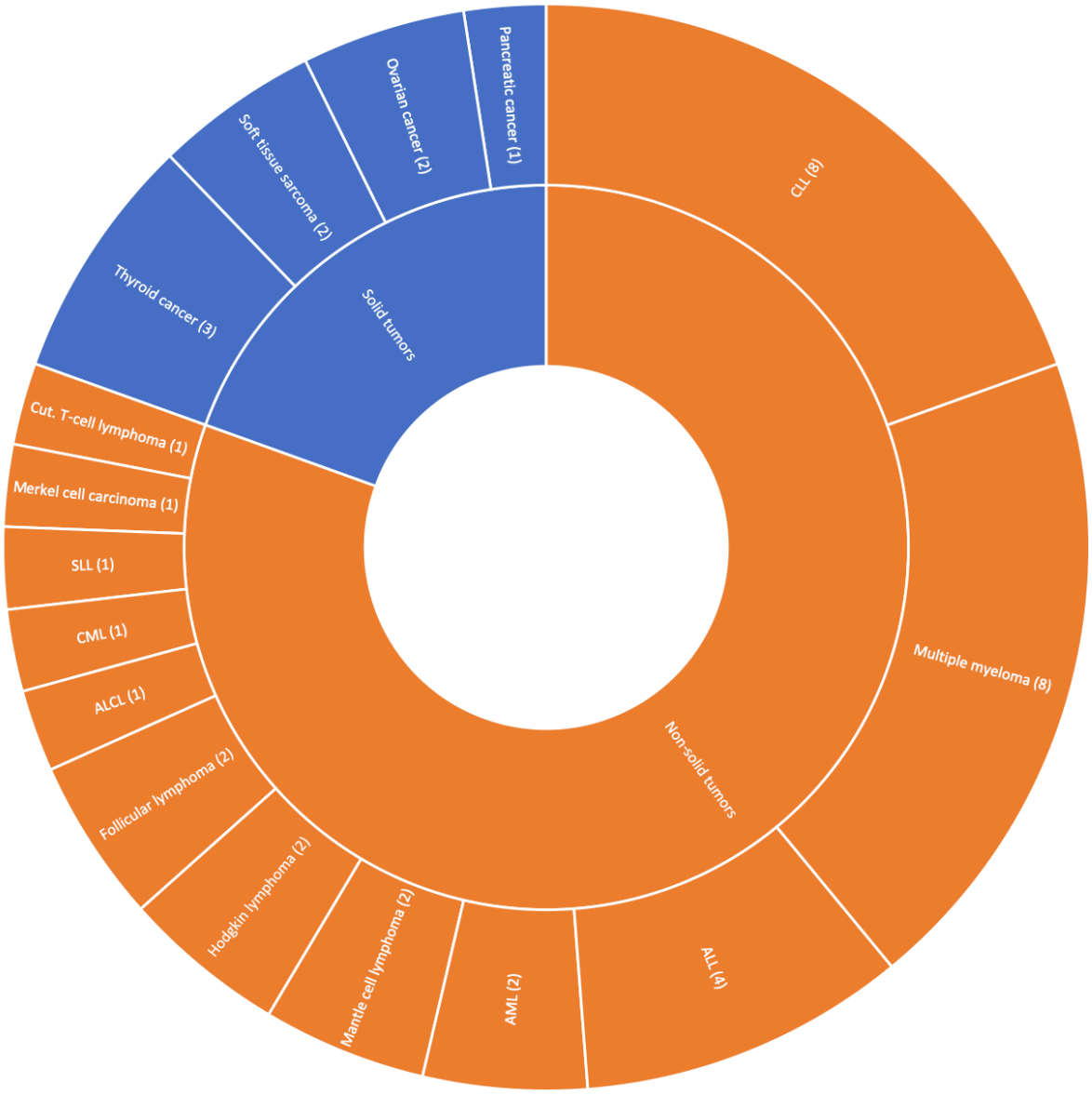
X-axis: year of marketing approval by the FDA and EMA; y-axis: number of approved biomarker-derived cancer indications with orphan drug designation; blue = Approved biomarker-derived cancer indications with orphan designation by the FDA; orange = Approved biomarker-derived cancer indications with orphan designation by the EMA.

Figure 3. FDA-approved solid and non-solid tumor cancer drug indications with Orphan Drug Act designation.



ALL = acute lymphoblastic leukemia; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; NSCLC = non-small cell lung cancer.

Figure 4. FDA- and EMA-approved solid and non-solid tumor cancer drug indications with Orphan Drug Act designation.



ALCL = anaplastic large cell lymphoma; ALL = acute lymphoblastic leukemia; AML = acute myeloid lymphoma; CLL = chronic lymphocytic lymphoma; CML = chronic myeloid lymphoma; SLL = small lymphocytic lymphoma; cut. T-cell lymphoma = Cutaneous T-cell lymphoma.

	Cancer Drug Indications with Orphan Designation by the FDA (2008 - 2017) and Comparison with the EMA					
	FDA				**EMA**	
	Generic Name	**Trade Name**	**Marketing Approval Date**	**Designation**	**Orphan drug Status**	**Approval Date**
1	**nivolumab**	Opdivo	12/20/2017	Treatment of Stage IIb to IV melanoma	no	06/28/2018
2	**bosutinib**	Bosulif	12/19/2017	Treatment of chronic myelogenous leukemia	no	04/23/2018
3	**obinutuzumab**	Gazyva	11/16/2017	Treatment of follicular lymphoma	yes	09/18/2017
4	**Brentuximab vedotin**	Adcetris	11/09/2017	Treatment of primary cutaneous CD30-positive T-cell lymphoproliferative disorders	yes	12/15/2017
5	**dasatinib**	Sprycel	11/09/2017	Treatment of chronic myelogenous leukemia	no	07/02/2018
6	**alectinib**	Alecensa	11/06/2017	Treatment of ALK-positive non-small cell lung cancer	no	12/18/2017
7	**acalabrutinib**	Calquence	10/31/2017	Treatment of mantle cell lymphoma	no approval	
8	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of follicular lymphoma	no approval	
9	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of diffuse large B-cell lymphoma	no approval	
10	**axicabtagene ciloleucel**	Yescarta	10/18/2017	Treatment of primary mediastinal B-cell lymphoma	no approval	
11	**pembrolizumab**	Keytruda	09/22/2017	Treatment of gastric cancer, including gastroesophageal junction adenocarcinoma	no approval	
12	**nivolumab**	Opdivo	09/22/2017	Treatment of hepatocellular carcinoma	no approval	
13	**copanlisib**	Aliqopa	09/14/2017	Treatment of follicular lymphoma	no approval	
14	**Gemtuzumab ozogamicin**	Mylotarg	09/01/2017	Treatment of acute myeloid leukemia	yes	04/19/2018
15	**Tisagenlecleucel**	Kymriah	08/30/2017	For the treatment of Acute Lymphoblastic Leukemia	no approval	

16	**inotuzumab ozogamicin**	Besponsa	08/17/2017	Treatment of B-cell acute lymphoblastic leukemia	yes	06/29/2017
17	**olaparib**	Lynparza	08/17/2017	Treatment of primary peritoneal cancer	no	12/16/2014
18	**olaparib**	Lynparza	08/17/2017	Treatment of ovarian cancer	no	12/16/2014
19	**olaparib**	Lynparza	08/17/2017	Treatment of Fallopian Tube Cancer	no	12/16/2014
20	**Cytarabine:daunorubicin liposome injection**	Vyxeos	08/03/2017	Treatment of acute myeloid leukemia	no approval	
21	**enasidenib**	Idhifa	08/01/2017	Treatment of acute myelogenous leukemia	no approval	
22	**ipilimumab**	Yervoy	07/21/2017	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no	05/31/2018
23	**daratumumab**	Darzalex	06/16/2017	Treatment of multiple myeloma	no approval	
24	**ceritinib**	Zykadia	05/26/2017	Treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase(ALK)-positive	no	06/23/2017
25	**brigatinib**	Alunbrig	04/28/2017	Treatment of anaplastic lymphoma kinase-positive (ALK+), c-ros 1 oncogene positive (ROS1+), or epidermal growth factor receptor positive (EGFR+) non-small cell lung cancer (NSCLC).	no approval	
26	**midostaurin**	Rydapt	04/28/2017	Treatment of acute myeloid leukemia	yes	09/18/2017
27	**regorafenib**	Stivarga	04/27/2017	Treatment of hepatocellular carcinoma	no	08/02/2017
28	**nivolumab**	Opdivo	04/25/2017	Treatment of Hodgkin lymphoma	no approval	
29	**methotrexate oral solution**	Xatmep	04/25/2017	Treatment of acute lymphoblastic leukemia in pediatric patients (0 through 16 years of age)	no	03/29/2017
30	**niraparib**	Zejula	03/27/2017	Treatment of ovarian cancer	yes	11/16/2017
31	**avelumab**	Bavencio	03/23/2017	Treatment of merkel cell carcinoma.	yes	09/18/2017
32	**pembrolizumab**	Keytruda	03/14/2017	Treatment of Hodgkin lymphoma	no	05/02/2017

33	**lenalidomide**	Revlimid	02/22/2017	Treatment of multiple myeloma	yes	02/23/2017
34	**ibrutinib**	Imbruvica	01/18/2017	Treatment of patients with extranodal marginal zone lymphoma (mucosa associated lymphoid tissue [MALT type] lymphoma)	no approval	
35	**ibrutinib**	Imbruvica	01/18/2017	Treatment of splenic marginal zone lymphoma	no approval	
36	**ibrutinib**	Imbruvica	01/18/2017	Treatment of nodal marginal zone lymphoma	no approval	
37	**rucaparib**	Rubraca	12/19/2016	Treatment of ovarian cancer	yes	05/24/2018
38	**bevacizumab**	Avastin	12/06/2016	Therapeutic treatment of patients with ovarian cancer	no	02/06/2017
39	**bevacizumab**	Avastin	12/06/2016	Treatment of fallopian tube carcinoma	no	02/06/2017
40	**bevacizumab**	Avastin	12/06/2016	Treatment of primary peritoneal carcinoma.	no	02/06/2017
41	**daratumumab**	Darzalex	11/21/2016	Treatment of multiple myeloma	yes	04/28/2017
42	**olaratumab**	Lartruvo	10/19/2016	Treatment of soft tissue sarcoma	yes	11/09/2016
43	**nivolumab**	Opdivo	05/17/2016	Treatment of Hodgkin lymphoma	no	06/19/2015
44	**ibrutinib**	Imbruvica	05/06/2016	Treatment of small lymphocytic lymphoma	yes	06/26/2016
45	**afatinib**	Gilotrif	04/15/2016	Treatment of non-small cell lung cancer with squamous histology.	no	03/31/2016
46	**venetoclax**	Venclexta	04/11/2016	Treatment of chronic lymphocytic leukemia	yes	12/05/2016
47	**crizotinib**	Xalkori	03/11/2016	Treatment of ALK-positive, MET-positive, or ROS-positive non-small cell lung cancer	no	08/25/2016
48	**ibrutinib**	Imbruvica	03/04/2016	Treatment of chronic lymphocytic leukemia (CLL)	yes	05/26/2016
49	**everolimus**	Afinitor	02/26/2016	Treatment of neuroendocrine tumors of gastroinstestinal or lung origin	no	05/26/2016
50	**obinutuzumab**	Gazyva	02/26/2016	Treatment of follicular lymphoma	yes	06/13/2016

51	**eribulin mesylate**	Halaven	01/28/2016	Treatment of soft tissue sarcoma	no	05/02/2016
52	**ofatumumab**	Arzerra	01/19/2016	Treatment of chronic lymphocytic leukemia	yes	12/08/2016
53	**pembrolizumab**	Keytruda	12/18/2015	Treatment of Stage IIB through IV malignant melanoma	no	07/17/2015
54	**alectinib**	Alecensa	12/11/2015	Treatment of ALK-positive non-small cell lung cancer	no	02/16/2017
55	**bendamustine for 50ml admixture**	Bendeka	12/07/2015	Treatment of Follicular Lymphoma, Small Lymphocytic Lymphoma, Lymphoplasmacytic Lymphoma, Splenic Marginal Zone Lymphoma, Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoma Tissue (MALT), and Nodal Marginal Zone Lymphoma (Collectively Indolent B-cell Non-Hodgkin's Lymphoma)	no approval	
56	**bendamustine for 50 ml admixture**	Bendeka	12/07/2015	Treatment of chronic lymphocytic leukemia	no approval	
57	**elotuzumab**	Empliciti	11/30/2015	Treatment of multiple myeloma	no	05/11/2016
58	**necitumumab**	n/a	11/24/2015	Treatment of squamous non-small cell lung cancer	no	02/15/2016
59	**ixazomib citrate**	Ninlaro	11/20/2015	Treatment of multiple myeloma	yes	11/21/2016
60	**daratumumab**	Darzalex	11/16/2015	Treatment of multiple myeloma	yes	05/20/2016
61	**osimertinib**	Tagrisso	11/13/2015	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	no	02/02/2016
62	**cobimetinib**	Cotellic	11/10/2015	Treatment of stage IIb, IIc, III, and IV melanoma with BRAFV600 mutation	no	11/20/2015
63	**ipilimumab**	Yervoy	10/28/2015	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no approval	
64	**talimogene laherparepvec**	Imlygic	10/27/2015	Treatment of stage IIb-stage IV melanoma	no	12/16/2015
65	**trabectedin**	Yondelis	10/23/2015	Treatment of soft tissue sarcoma	yes	09/17/2007

66	**irinotecan liposome injection**	n/a	10/22/2015	Treatment of pancreatic cancer	yes	10/14/2016
67	**brentuximab vedotin**	Adcetris	08/17/2015	Treatment of Hodgkin's lymphoma	yes	06/24/2016
68	**gefitinib**	Iressa	07/13/2015	Treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer	no	06/24/2009
69	**dinutuximab**	Unituxin	03/10/2015	Treatment of neuroblastoma	withdrawal	08/14/2015
70	**panobinostat**	Farydak	02/23/2015	Treatment of multiple myeloma	yes	08/28/2015
71	**lenalidomide**	Revlimid	02/17/2015	Treatment of multiple myeloma	yes	02/19/2015
72	**lenvatinib**	Lenvima	02/13/2015	Treatment of follicullar, medullary, anaplastic, and metastatic or locally advanced papillary thyroid cancer	yes	05/28/2015
73	**nivolumab**	Opdivo	12/22/2014	Treatment of Stage IIb to IV melanoma	no approval	
74	**olaparib**	Lynparza	12/19/2014	Treatment of ovarian cancer	no	12/16/2014
75	**lanreotide acetate**	Somatuline Depot	12/16/2014	Treatment of neuroendocrine tumors	no approval	
76	**blinatumomab**	Blincyto	12/03/2014	Treatment of acute lymphocytic leukemia	yes	11/23/2015
77	**bevacizumab**	Avastin	11/14/2014	Treatment of fallopian tube carcinoma	no	07/31/2014
78	**bevacizumab**	Avastin	11/14/2014	Treatment of primary peritoneal carcinoma.	no	07/31/2014
79	**bevacizumab**	Avastin	11/14/2014	Therapeutic treatment of patients with ovarian cancer	no	07/31/2014
80	**ramucirumab**	Cyramza	11/05/2014	Treatment of gastric cancer	no	12/19/2014
81	**bortezomib**	Velcade	10/08/2014	Treatment of mantle cell lymphoma.	no	01/30/2015
82	**pembrolizumab**	Keytruda	09/04/2014	Treatment of Stage IIB through IV malignant melanoma	no	07/17/2015
83	**ibrutinib**	Imbruvica	07/28/2014	Treatment of chronic lymphocytic leukemia (CLL)	yes	05/26/2016

84	**idelalisib**	Zydelig	07/23/2014	Treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma	no	09/18/2014
85	**idelalisib**	Zydelig	07/23/2014	Treatment of follicular lymphoma	no	09/18/2014
86	**Belinostat**	Beleodaq	07/03/2014	Treatment of peripheral T-cell lymphoma (PTCL)	not yet approved	
87	**ceritinib**	Zykadia	04/29/2014	Treatment of patients with non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase(ALK)-positive	no	05/06/2015
88	**mercaptopurine oral solution**	Purixan	04/28/2014	Treatment of acute lymphoblastic leukemia in pediatric patients	yes	03/09/2012
89	**ramucirumab**	Cyramza	04/21/2014	Treatment of gastric cancer	no	12/19/2014
90	**ofatumumab**	Arzerra	04/17/2014	Treatment of chronic lymphocytic leukemia	yes	06/30/2014
91	**ibrutinib**	Imbruvica	02/12/2014	Treatment of chronic lymphocytic leukemia (CLL)	yes	10/21/2014
92	**trametinib and dabrafenib**	Mekinist And Tafinlar	01/09/2014	Treatment of Stage IIb through IV melanoma.	no	08/25/2015
93	**sorafenib**	Nexavar	11/22/2013	Treatment of medullary thyroid cancer, anaplastic thyroid cancer, and recurrent or metastatic follicular or papillary thyroid cancer	yes	05/23/2014
94	**ibrutinib**	Imbruvica	11/13/2013	Treatment of mantle cell lymphoma	yes	10/21/2014
95	**obinutuzumab**	Gazyva	11/01/2013	Treatment of chronic lymphocytic leukemia	yes	07/23/2014
96	**paclitaxel protein-bound particles**	Abraxane	09/06/2013	Treatment of pancreatic cancer.	no	12/02/2013
97	**afatinib**	Gilotrif	07/12/2013	Treatment of epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC).	no	09/25/2013
98	**denosumab**	Xgeva	06/13/2013	Treatment of patients with giant cell tumor of bone	no	09/01/2014
99	**lenalidomide**	Revlimid	06/05/2013	Treatment of mantle cell lymphoma	yes	07/08/2016
100	**trametinib**	Mekinist	05/29/2013	Treatment of Stage IIb through Stage IV melanoma	no	06/30/2014

101	**dabrafenib**	Tafinlar	05/29/2013	Treatment BRAF V600 mutation positive Stage IIB through IV melanoma	no	08/26/2013
102	**regorafenib**	Stivarga	02/25/2013	Treatment gastrointestinal stromal tumors	no	07/28/2014
103	**pomalidomide**	Pomalyst	02/08/2013	Treatment of multiple myeloma	yes	08/05/2013
104	**imatinib**	Gleevec	01/25/2013	Treatment of Philadelphia-positive acute lymphoblastic leukemia	no	06/27/2013
105	**ponatinib**	Iclusig	12/14/2012	Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL)	yes	7/01/2013
106	**ponatinib**	Iclusig	12/14/2012	Treatment of chronic myeloid leukemia	yes	07/01/2013
107	**cabozantinib**	Cometriq	11/29/2012	Treatment of follicular, medullary and anaplastic thyroid carcinoma and metastatic or locally advanced papillary thyroid cancer.	yes	03/21/2014
108	**omacetaxine mepesuccinate**	Synribo	10/26/2012	Treatment of chronic myelogenous leukemia	withdrawal	
109	**bosutinib**	Bosulif	09/04/2012	Treatment of chronic myelogenous leukemia	no	02/22/2018
110	**vinCRIStine sulfate LIPOSOME injection**	Marqibo	08/09/2012	Treatment of acute lymphoblastic leukemia	no approval	
111	**carfilzomib**	Kyprolis	07/20/2012	Treatment of multiple myeloma	yes	11/19/2015
112	**pazopanib**	Votrient	04/26/2012	Treatment of soft tissue sarcomas	no	08/03/2012
113	**Erwinia L-asparaginase**	Erwinase	11/18/2011	Treatment of acute lymphocytic leukemia.	no approval	
114	**brentuximab vedotin**	Adcetris	08/19/2011	Treatment of Hodgkin's lymphoma	yes	06/24/2016
115	**brentuximab vedotin**	Adcetris	08/19/2011	Treatment of anaplastic large cell lymphoma	yes	10/25/2012
116	**vemurafenib**	Zelboraf	08/17/2011	Treatment of patients with IIb to Stage IV melanoma positive for the BRAF(v600) mutation	no	02/17/2012
117	**romidepsin**	Istodax	06/16/2011	Treatment of non-Hodgkin T-cell lymphomas	refusal	02/12/2013

118	**everolimus**	Afinitor	05/05/2011	Treatment of neuroendocrine tumors of pancreatic origin	no	08/24/2011
119	**levoleucovorin**	Fusilev	04/29/2011	For use in combination chemotherapy with the approved agent 5-fluorouracil in the palliative treatment of metastatic adenocarcinoma of the colon and rectum	withdrawal	
120	**vandetanib**	Caprelsa(R)	04/06/2011	Treatment of patients with follicular thyroid carcinoma, medullary thyroid carcinoma, anaplastic thyroid carcinoma, and locally advanced and metastatic papillary thyroid carcinoma	no	02/17/2012
121	**peginterferon alfa-2b**	Sylatron	03/29/2011	Treatment of malignant melanoma stages IIb through IV.	no	03/09/2010
122	**ipilimumab**	Yervoy	03/25/2011	Treatment of high risk Stage II, Stage III, and Stage IV melanoma	no	07/13/2011
123	**crizotinib**	Xalkori	03/11/2011	Treatment of ALK-positive, MET-positive, or ROS-positive non-small cell lung cancer	no	10/23/2012
124	**trastuzumab**	Herceptin	10/20/2010	Treatment of HER2-overexpressing advanced adenocarcinoma of the stomach, including gastroesophageal junction	no	01/19/2010
125	**rituximab**	Rituxan	02/18/2010	Treatment of chronic lymphocytic leukemia	no	06/15/2017
126	**ofatumumab**	Arzerra	10/26/2009	Treatment of chronic lymphocytic leukemia	yes	04/19/2010
127	**pralatrexate**	Folotyn	09/25/2009	Treatment of T-cell lymphoma	refusal	06/21/2012
128	**bevacizumab**	Avastin	07/31/2009	Treatment of renal cell carcinoma	no	01/12/2005
129	**bevacizumab**	Avastin	05/05/2009	Treatment of malignant glioma	not approved	
130	**imatinib mesylate**	Gleevec	12/19/2008	Treatment of gastrointestinal stromal tumors	no	04/29/2009
131	**Fludarabine phosphate oral tablets**	n/a	12/18/2008	Treatment of B-cell chronic lymphocytic leukemia	approved decentralized system (national level)	

132	**bendamustine hydrochloride**	Treanda	10/31/2008	Treatment of Follicular Lymphoma, Small Lymphocytic Lymphoma, Lymphoplasmacytic Lymphoma, Splenic Marginal Zone Lymphoma, Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoma Tissue (MALT), and Nodal Marginal Zone Lymphoma (Collectively Indolent B-cell Non-Hodgkin's Lymphoma)	approved decentralized system (national level)	
133	**bortezomib**	Velcade	06/20/2008	Treatment of multiple myeloma	no	08/29/2008
134	**Bendamustine hydrochloride**	Treanda	03/20/2008	Treatment of chronic lymphocytic leukemia	approved decentralized system (national level)	
135	**Levoleucovorin**	Fusilev	03/07/2008	For use in conjunction with high-dose methotrexate in the treatment of osteosarcoma.	withdrawal	

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3, 4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	3
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3, 4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*3, 4*
Bias	9	Describe any efforts to address potential sources of bias	3-5
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3-5
		(*b*) Describe any methods used to examine subgroups and interactions	3-5
		(*c*) Explain how missing data were addressed	3-5
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	135 drugs
		(b) Give reasons for non-participation at each stage	3
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	3
		(b) Indicate number of participants with missing data for each variable of interest	3
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	*3*
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	NA
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	4-6
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	6
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	5-6
Generalisability	21	Discuss the generalisability (external validity) of the study results	5-6
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.